A STUDY OF
MALARIA AND BERI-BERI

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BY

S. M. VARIS, M D., C M (EDIN)

*Author of Digest of Human Physiology , Late Plague Medical Officer of
U P and Oudh (1902) , Member of B M A*

*CONTRIBUTIONS — Tubercular Hip Joint , Milk and Microbes ; Mental Fatigue in
Children , Danger of Sewage to Public Health , Fly as a Cause of Infantile
Diarrhœa and Warfare on Flies ; Etiology, Epidemiology and
Prophylaxis of Malaria , Paper on Beri Beri to
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MEMENTO

TO THE OCCASION OF THE

CORONATION DURBAR IN DELHI, 1911,

Of His Imperial Majesty King George the Fifth King
of the United Kingdom of Great Britain and
Ireland and of the British Dominions
beyond the Seas, Defender of the
Faith, Emperor of India, **and**
Her Imperial Majesty the
Queen-Empress.

DEDICATED

TO

THE HON'BLF COL. C. C. MANIFOLD, I.M.S., M.D., ETC.,

INSPECTOR-GFNERAL OF CIVIL HOSPIIALS OF

U. P. AND OUDH

WHO HAS DONF SO MUCH TO BRING THE OFFICIAL AND NON-
OFFICIAL MEDICAL PRACTITIONERS TOGETHER
AND TO IMPROVE THE PROFESSION.

PREFACE.

(By the Author.)

The present is a time of the greatest national rejoicing for the Indian people. I consider it a happy omen that the publication of this work should coincide with such an auspicious event as the epoch-making visit of their Imperial Majesties the King-Emperor and Queen-Empress to this country.

It has stirred the hearts of the people to their inmost depths and has evoked most genuine sentiments of devotion and loyalty.

The sympathy of the reigning house of England for the poor and the afflicted is proverbial. The memory of the late King Edward is associated with many an institution designed for the alleviation of human suffering and the sympathies of our present Sovereign (May he live long) are no less marked in this direction.

The Government of India have shown an equal solicitude for the protection of the lives of the countless millions entrusted to their charge as steps are constantly being taken to avert the ravages of plague as well as to prevent the outbreak of other epidemics. Nor have they been behind the other Governments of the world in directing attention towards Malarial disease. Not long ago, in 1909, a conference was held at Simla with a view to determine the Etiology, Epidemiology and Prophylaxis of Malaria when it was decided to form Investigation Committees in different Provinces. They have already started work and their labours are likely to result in no little good to the suffering population of India.

GENERAL REMARKS.

Malaria reigns all over India.   Where it is not epidemic, it appears in endemic form.   Cases have been noticed even in places which are supposed to be free from it on account of their situation and healthy surroundings.   Undoubtedly heavy as has been the mortality from plague during the last few years, it has been barely half as much as that from fever.   The growing severity in the outbreak of Malaria has lately caused much attention and interest to be centred on it.   In my opinion the disease is so important and extensive in its scope as to surpass any other in the whole science and practice of medicine in interest from a technical point of view.   There may be millions of people in India who may be harbouring the parasites in their body, but it is not possible with the assistance of the best microscope to eliminate the parasites from the peripheral circulation.   It is man and not the mosquito in all cases that conveys Malaria.   In this country there exist peculiarly favourable conditions for the propagation of its germs, namely, the insanitary habits of the people, their unhealthy surroundings and, in addition to these, methods of treatment which are by no means in conformity with the progress of Medical science   These are very malignant sores for Medical men to remove from the site.   Until the indigenous growth of scientific men receives stimulus from the State, these are likely to remain an obstinate feature of the land hindering the work of modern science. The theory of the dissemination of Malaria through the mosquito is ridiculed not only by the ordinary layman, but often by well educated people as well as by those who pro· fess to dabble in the art of healing on a system of their own.

Malaria is not one disease but a series of conditions differing widely in their clinical features which baffle diagnosis and demand different lines of treatment.   All these are grouped under the name of Malaria   " With the

banishment of Malaria a new era will dawn in India's
history." These words uttered a short time ago by a
distinguished personage heightened the importance of the
disease as being chiefly responsible for the high death-rate
prevalent in the country. Before that aim can be achieved,
the disease is likely to continue to claim a heavy toll of
human life. The Malarial germs play havoc with the red
corpuscles of the blood destroying and consuming their
hœmoglobin. At the same time they produce a poison that
devours the whole system and reduces the physical and
mental strength to the lowest ebb, setting up changes which
lead to other diseases of the important organs. It is neces-
sary in the public interest to point out clearly how the evil
effects of the disease in all their diverse manifestations may
be overcome ; how the patient may completely recover his
health and strength and be protected against further attacks.
The early treatment and diagnosis of the disease are simple
and well known. One takes a few doses of quinine and
shakes off the fever. It is the after-treatment and guarding
against recurrence which demand special care and attention.
The neglect of the latter makes the initial attack assume
gradually worse and more severe forms which prove
tenacious.

APOLOGY FOR THE BOOK.

There exist a number of text-books on the causes and
treatment of Malaria by original investigators, but they have
been published in foreign countries and are not within the
reach of the majority of my countrymen. I have had
opportunities of studying the disease at notoriously malarious
places and had much to do with it during the terrible epi-
demic of 1908-09 My observations are based on thirteen
years' experience of the disease. Encouraged by the success
which has always attended my treatment, I venture to em-
body the knowledge thus gained in this work, with a view

to help the public and junior brother practitioners. My object is to eradicate old prejudices and to combat the antagonism which exists among my countrymen in regard to latest methods of treatment. A work of this kind by an Indian is likely to go far towards popularising remedies upon which the people have hitherto looked askance. It may also lead indirectly to the establishment of a sound school of medicine and may bring the people on a level with the civilised portions of the globe in matters hygienic.

AUTHOR'S DIFFICULTY.

While enaged on this work I have often been weighed down by the feeling that the task was too difficult for me to accomplish. There are no facilities in this country for bringing out a scientific work. One has to depend a great deal upon one's own resources. There is a sad want of well-equipped libraries and laboratories, and periodicals on recent medical research are only a sight for sore-eyes. The justification for the publication of the book may be looked for and found in the book itself. It does not pretend to be original in its entire form, but there is matter which the author may claim to be his own, and would request the indulgent reader to judge the work as a whole.

SPECIAL FEATURES OF THE BOOK.

It provides a practical study of the diagnosis, treatment and recurring attacks of fever due to Malaria. It gives fuller and clearer account of the recrudescence of the disease than any other book written on the subject. One especial chapter has been drawn up for the guidance of medical practitioners. The chapter on Epidemiology and Prophy-laxis has reference to conditions of life in India which may prove of interest to medical officials.

I have given a short account of Beri-Beri along with Malaria on the ground that it is threatening to become a

prevailing disease in some parts of the country, and it is equally important to have some knowledge of it.

CONCLUSION.

I cannot refrain from expressing my deep gratefulness to Rani Surat Kunwar Saheba, of Khairigarh, to whose generous assistance the book owes its birth. The kindly encouragement offered to me indicates her keen desire to relieve suffering as well as her sense of appreciation of the progress needed in the country. She is a thoroughly enlightened lady who has kept pace with the times. As her family physician, I am constantly called upon to visit her estate which borders on the Terai and is infested by Malaria. I had greater opportunities of carrying on my researches there than elsewhere I am also much indebted to Rai Bahadur Kuar Bam Bahadur Shah Saheb, Manager of the Estate, for the help I have received from him. He is universally admired for his kind-heartedness and charm of manners.

I offer my heartiest thanks to the Honourable Colonel C. C. Manifold, I.M S , Inspector-General of Civil Hospitals of the United Provinces of Agra and Oudh, for having been able to spare some of his precious time to write an introduction for this book. During my short acquaintance with him, I have been much impressed by his genuine courtesy and sympathetic attitude towards Indians. His popularity among the subordinate ranks of the service testifies to these qualities.

LUCKNOW :   S. M VARIS.

5th October 1911.

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ERRATA.

1. Page 6, para. 1st, line 10, "*hylaine*" ought to be "*hyaline.*"
2. „ 7, line 1, "*terrior*," ought to be "*terror*"
3. „ 17, para. 1st, line 21, "*an*" ought to be "*and.*"
4. „ 23, para. 1, line 33, "*irating*" ought to be "*irritating.*"
5. „ 146, last para., "*Anennæ*" ought to be "*antennæ.*"
6. „ 360, line 14, para. 2nd, "*Bubinat*" ought to be "*Rubinat.*"
7. „ 362, line 9, para. 3rd, "*Hydrotherophy*" ought to be "*Hydrotheraphy.*"
8. „ 130, line 22, para. 2nd, "*odies*" ought to be "*bodies.*"
9. „ 135, line 33, para. 2nd, "*severa*" ought to be "*several.*"
10. „ 137, line 3, para. 1st, "*do,*" unnecessary.
11. „ 139, line 23, para. 4th, '*have*" ought to be "*leave.*"
12. „ 168, line 25, para. 1st, "*they,*" one is unnecessary.
13. „ 190, line 8, para. 2nd, "*wells-tudied*" ought to be "*well studied.*"
14. „ 216, line 4, para. 2nd, "*Ile Arnstein*)" ought to be "*He (Arns tein).*"
15. „ 222, line last, para. 2nd, "*denonstrable*" ought to be "*demonstrable.*"
16. „ 237, line 8th, para. 1st, "*æstiva*" ought to be "*æstival.*"
17. „ 247, line 17, para. 1st, "*Parasite æstivo-autumnal)*" ought to be *Parasite (æstivo-autumnal).*"
18. „ 283, line 3, para. 1st, "*(cited by Lowron Col at, studying* ought to be "*(cited............Col. Cit.)*"
19. „ 150, line 12, para. 1st, 66 "*very excessive*" ought to be "*very excessive.*'

MALARIA AND BERI-BERI.

INTRODUCTION

By

THE HON'BLE COL. C C. MANIFOLD, M.D., I.M.S.,

Inspector-General of Civil Hospitals of U P. and Oudh

The advances made in Medical Science during recent years have been very great; especially has this been the case in Tropical Medicine. Since Major Sir Ronald Ross of the Indian Medical Service and Sir Patrick Manson published the result of their far reaching researches in Malaria, the principles of their methods of investigation have been applied to one tropical disease after another, always with profit and usually with success in discovering the ultimate cause of the disease. So wide a branch of medicine has this become that we hear now of chairs established in European Medical Schools in Tropical Medicines in Parasitology, Protozoology, and even in Helminthology, subjects that a few years back were considered merely as minor branches of Zoology. The study of the mosquito alone may be the life work of some men.

In these highly specialised branches of Pathology, increasing as they are in complexity as well as in number, it is little wonder if the medical practitioner has been unable to keep pace with the advancement of his brethren who work in the Laboratory. For although the Pioneers of Tropical Medicine as Ross, Manson, and many others were but general practitioners, who saw more clearly than their fellows, the more modern researches have been for the most part carried out by highly trained laboratory workers, who are in fact specialists in Pathology. This specialisation

has necessitated a separation to a large extent of the work of the pathologist from that of the clinician, a separation in many respects to be regretted. It is good therefore that at times a practitioner should come forward to correlate the laboratory and the clinical aspects of a disease and apply the teachings of the former to the daily practice of the physician. Moreover, it is necessary that at times one should explain to his brother practitioners what has been going on in the pathological world, and what advances the laboratory has recently made, and how these advances may help them.

Both of these things Dr. Varis attempts in this book, and it is very much to his credit that among the busy moments of a practitioner's life he has been able to find time after reading as deeply as he evidently has done to work practically at his subject both in the laboratory and at the bedside, and to publish his experiences.

In the treatment of disease the keynote of success is accurate diagnosis, a thing that can only be obtained in Tropical Medicine by knowledge of both laboratory and clinical methods and by close observation of the patient. But a knowledge of the facts contained in this book should take one further than the mere treatment of malaria : it should lead to the prevention of that disease as well as of others. It is in the dissemination of knowledge for the prevention of sickness by measures especially adopted for each disease and more especially by methods of general sanitation that the chief hope of a lessened death-rate in India lies, and the generation now growing up in these Provinces should, by the time they reach manhood, be able to show the vital statistics of the country better than ever they have been before.

Dr. Varis belongs to the United Provinces of India and to a generation which had to seek its medical education outside their limits. He sought it in Europe where he

took a British University degree with distinction, and as this work shows has applied the scientific knowledge there attained to good purpose in Tropical Medicine. We have now established in our midst in these United Provinces a Medical College, inferior to none and which will form a centre from which the light of Preventive and Remedial Science will radiate and penetrate into every dark corner.

Such books as this one Dr. Varis has written will give a line of work and thought to the coming generation of Graduates in Medicine, who more fortunately placed can now secure their medical education without going outside their territorial limits

C. C. MANIFOLD.

MALARIA.

CHAPTER I.

DEFINITION.

Malaria is a disease of parasitical origin characterised by splenic enlargement, brief febrile attacks which recur periodically, melanæmia, and a tendency in protracted cases to irregular fever and extreme anæmia.

The most characteristic material manifestations are intermittent or remittent fever, certain forms of disease described as "pernicious," and a chronic cachexia with enlargement of the spleen and anæmia.

ETYMOLOGY.

Applied originally to the miasm or poison which was supposed to produce the disease, the name "Malaria" was derived from the Italian "mal' aria," and signified "bad air." It is now used to designate the disease itself for which purpose it is more convenient than any other.

SYNONYMS.

Various names have from time to time been applied to the disease under consideration, of which the following are the best known :—

Chills and *fever ; Malarial fever ; Intermittent fever ; Fever and ague ; Paludism* or *paludal fever ; Swamp* or *Marsh fever ; Autumnal fever ; Miasmatic fever ; Periodical fever; Walcherin fever ; Batavian fever ; Hungarian fever ; African fever ; Panama fever*, and *Chagres fever* are names derived from localities where the disease has prevailed with special intensity ; but they are only in occasional use. Finally, *Remittent fever Bilious Remittent fever, Hæmorrhagic Remittent fever, Congestive fever, Dumb ague, Black water*

fever, *Black jaundice*, etc., are special names that have been applied to certain types or manifestations of the disease.

HISTORY.

There are few diseases with which our profession has been longer acquainted than with malaria : in fact, the history of this disease reaches back to the earliest period of medical science.   Not only were the common forms then well known, but also, and particularly, the uncommon and the pernicious varieties of the malady.

Protagoras describes the drowsiness accompanying intermittent fever, and the tetanus which sometimes supervenes, and tells of many cases that have terminated fatally, whence it may appear that he may have been the first to observe pernicious intermittent fever (*febris int. comitata*).   Delsus draws the distinction between *quotidian*, *tertian*, and *quartan* fever, and refers to the possibility of a longer intermission in these words: " *Interdum etiam longiore circitû quædam redeunt, sed it raro evenit.*"   He also speaks of the genus "emitritation," which he describes as a fever lasting three days, with uncommonly long paroxysms reaching into one another.

Archigenes was the first writer who recognised the complex nature of the *hemi-tritæa*, or *semi-tertian* form, as consisting of a tertian and a quotidian fever combined.   He also makes mention of masked intermittents, especially when appearing in the form of dysentery or diabetes.   Rhazes, the Arabian, gives an account of *febris subintrans*.   Ebu Sina saw that rare type in which the fever occurs every sixth or seventh day, and Valescus, of Taranta, refers to a fever recurring every thirtieth day (Philos. Pharmaceut, et Chirurg. Lib. *v.* Ed. Hartmann Beyer, Francf., 1699).   Rembert Dodöeus describes that form of intermittent fever designated as " Katochus, " and Diamedes Cornarus first noticed combinations of the intermittent fever with dysentery or rather the intermittent form of the latter affection.

No considerable attention, however, was given to the study of malarial fever until after the introduction of the *cinchona bark* from Peru into Spain, in the year 1640, by the Viceroy del Cinchon and his body physician, Juon del Vego; and, indeed, this event marks an epoch in the history of medicine in its revolutionising influence upon medical doctrines. This study was stimulated in part by the conflicting results following the use of the new drug, and in part by the obstinate manner in which physicians generally clung to the old theories of Galen. No truly reliable results were reached in practise until after the apothecary's clerk, Robert Talbor, or Tabor, of Cambridge (Pyretology ; or a Rational Account of the Cause and Cure of Agues, etc., London, 1672), had introduced the uses of larger doses and more effective forms of administration (mostly macerations in wine or the tincture with or without opium, which preparation he sold extensively as a secret remedy for Ague) ; and until Sydenham conceived the idea of giving the cinchona immediately *after* the first attack, *during* the intermission, for the purpose of forestalling a subsequent paroxysm. He also pointed out the differences between vernal and autumnal intermittent fevers. Besides his works, the most notable upon this subject are those of Richard Morton, Torti, Ramazzini, and Lancisi : they remain to this day the great classics on malaria, containing as they do the fundamental clinical and therapeutical facts relating to this disease. Morton and Lancisi demonstrated clearly the relation of malaria to *marsh miasm.* Especially complete and keen in analysis is the *nosography* of Torti (Therapeutice Specialis ad Febres Quasdam Perniciosas, etc., Mutinæ, 1712), whose classifications of the malarial fevers, particularly of the pernicious and the mixed forms, has been followed by most subsequent authors.

The diagnostics as well as the therapeutic value of the Peruvian bark was recognised, and assisted materially in the discrimination of the malarial fevers from the other

so-called essential fevers. It is interesting to note the relative
accuracy of diagnosis and of description of the group of
malarial fevers from the latter half of the seventeenth century
onwards, in contrast to the confusion which existed regard-
ing the other essential fevers until the discrimination of
the latter by the pathological studies of our own time. In
the eighteenth centuries the military and the colonial enter-
prises of England served to extend the knowledge of the
geographical distribution of malaria, particularly in tropical
climates. The works of Pringle and of Lind contain especially
noteworthy observations on this point. But the great mass
of the very extensive literature on the *epidemiography* of mala-
rial disease, which has been so industriously collected and ably
analysed by Hirach (Handb. der Histor. Geograph ; Patho-
logie, Stuttgart, 1881) is of comparatively recent date. As
regards malaria, the significance of the active studies in
morbid anatomy of the first half of the nineteeth century
relates to the clear differentiation of typhoid fever from
malaria and other fevers, rather than to the actual contribu-
tions to the pathology of malaria, although these were not
lacking. The occurrence of enlarged spleens, so-called *fever-
cakes* or *ague-cakes*, and even the dark colour of the organs in
association with malarial fevers, had been occasionally ob-
served, notably by Lancisi, but it was not until the first half of
the last century that the intimate relation of these alterations to
malaria was definitely established. Congestion and enlarge-
ment of the spleen were emphasised by Audauard (1808,
1812, 1818) as the essential anatomical lesions of malarial
fever. Bailly, in 1825, noted, in a series of autopsies on
cases of pernicious malarial fever observed in Rome in 1822,
the dark colour of the cortical gray matter of the brain, and
the congestion of the cerebral meninges and substance. He
laid especial emphasis upon the evidences of supposed inflam-
mation of the central nervous system and of the stomach
and intestines. These anatomical observations, together with

those of Nepple (1828, 1835) and, to a less extent of
Maillot (1835), were interpreted in favour of Broussaisism,
which exerted such a malign influence upon professional
procedure at the period. In the United States of America,
valuable contributions to the pathology of malarial fevers,
especially of the remittent type were made, during the fourth
decade of the last century, by Stewardson (Philadelphia),
Swett (New York), and Anderson and Frick (Baltimore).

The first-mentioned observer demonstrated the bronzed
colour of the liver in malarial fevers, and regards this as the
characteristic anatomical criterion of the disease. His obser-
vations were confirmed and extended by the other writers
named, Alanzo Clark ; in 1855, he demonstrated that the
bronzed colour of these livers is due to the presence of granules
of yellow, brown, and black pigment, which he regarded as
derived from colouring matter of the red blood corpuscles.
The monumental work of Daniel Drake, on " The Principal
diseases of the Interior valley of North'America (1650—1854)
contains a large amount of valuable information based upon
personal observation and research, as to the distributions and
characters of the malarial fevers in the part of the country in
question indicated by the title of this work. It is interesting
to note, in the light of more recent discoveries, the ingenious
arguments advanced by Mitchell (on the Criptogamous Origin
of Malarious and Epidemic Fevers, 1849) in favour of the
doctrine of *contagium animatum.* This book deserves to
rank with the more frequently quoted work of Henle relating
to the same line of argument. The parasitic theory of
malaria was about the same time advocated in Italy by Bassi
and Raoori. The latter, in a discussion with the former,
writes :—" There is no objection to the belief that parasites of
intermittent fever, the first generation of which is exhausted
in the first periodical attack, may go on to the second
generation in the same body." Further on he adds :—"The
duration of the attacks is equal to the life of the parasites."

Heinrich Meckel was the discoverer of the malarial pigment, which he found and described, in 1848, in the blood and organs of the dead body of an insane patient. He was ignorant of the relation of this pigment to malaria. The next report concerning the pigment was, in 1849, made by Virchow, who observed the condition in the body of a man who had suffered from chronic malaria. There soon followed the observation of Heschel, Planner, A. Clarke, Tegri, Freriches, and others, fully establishing the relation of the pigment to malaria. The source of the pigment was regarded by Mechel and Virchow as in the spleen, and this doctrine was elaborated by Freriches.

Planner was the first (1854) who saw the pigment in the fresh blood of living patients, and he suggested that the pigment might be formed in the circulating blood, a view which Arnstein (1874) and Kelsch (1875) more fully presented and advocated subsequently. There appears every reason for supposing that some of the pigmented bodies which are now recognised as parasitic organisms had been seen by earlier observers without knowledge of their true nature. Thus, Michel noted the presence of pigment granules in colourless, hylaine bodies devoid of definite nuclei. He, and more particularly Virchow and Frerichs, observed pigments in fusiform and curved bodies in the blood, which, although interpreted as endothelial cells of splenic origin, in all probability were, at least in part, the crescentic forms of the parasite. Some of the largest pigmented spherical organisms must have been seen and mistaken for leucocytes bearing pigment granules. Confusion, however, reigned in spite of all this. Some forms of typhoid fever were held to be malarial ; some authorities held that dysentery and yellow fever were results of malaria ; in malarial regions complications of endemic infections with other diseases were seen, where they did not exist, and new diseases were created, such as *typho-malarial* fever The consequence of all

this was a terror of quinine, which was used to overcome the supposed malarial infection or complications to such an extent as to make the value of the drug a matter of serious doubt. In order to distinguish it from other infections the attempt was made, in the latest works on the malarial fever prior to the discovery of parasite chiefly by clinical observations, definitely to circumscribe the limits of the fever of malaria. The conviction, on the other hand, that a malarial parasite certainly existed had induced several investigators, in a short space of time and in various places, to institute researches in that direction.

After many vain efforts on the part of others, the malarial parasite was discovered by Laveran in November 1880, and this introduced a new era into our knowledge of the disease. Indeed, it has furnished an unfailing means of diagnosis of malarial affections, and materially advanced our ideas of their pathology, as well as led to a better understanding of their clinical phenomena and various types, furnished important data for progonsis and led to improvements in remedial procedures. But his discovery was not universally acknowledged for many years : not, indeed, until after the researches made in Italy had enriched the parasitology of malarial affections in man with new data. It is to the *protozoa* that the parasite thus discovered belonged, and not to the class the bacteria among which had been found many of the pathogenic agents of several infectious diseases. This was the first example of a *protozoic* infection in animals, although *phytopathology* had shown that there were plant diseases caused by analogous endocellular parasites. In many animals parasites like those of human malaria were later discovered. The so-called *Bacillus malariæ*, described in 1879 by Klebs and Tomas-i-Crudelli, which for a short period had a certain vague idea, chiefly with the Italian writers, never rested upon satisfactory observations which indicated that it bore any relation to malaria; and it deserves no more consideration

than the palmella of Salisbury, and the other alleged organ-
isms that prior to Laveran's discovery were from time to
time described.

CHAPTER II.

GEOGRAPHICAL DISTRIBUTION.

Although it is foreign to enter upon a minute investigation of the geographical distribution of malaria, yet it may be as well to mention here the most important foci of the disease.

So far as Europe is concerned one of the most famous malarial regions of Germany lies south of the Carpathian Mountains, embracing the major part of Hungary, what are called the greater and lesser Hungarian plains, Bant, Croatia, and a part of Slavonia. Not less extensive and notorious are the fevers of Dalmatia and Istria; while they prevail under a milder form in the great plain of the Danube in Lower Austria and in the marshes, as well as in the northern portion of Galicia. A second and very extensive malarial region exists in the North German flatlands : Northern Silesia, the plain of the River Mark, the Baltic coast of Prussia, Pomerania, and Meklenburgh ; the marsh and meadow regions of Hanover and Oldenburgh ; strips of the western coast of Holland and Schleswig ; the lowlands of Westphalia, as well as the marshy plains of the Rhine and its tributaries, including Holland, especially its seaboard provinces of Groningen, Friesland, North and South Holland and the long-famed Zealand ; furthermore, the northern and western provinces of Belgium, in those of west Flanders and Antwerp in particular. Malaria is entirely unknown, or occurs in only single localities (as in Rhinegau and the Danube bottom-lands of Würtemburgh and Bavaria) in the mountainous regions of Upper Austria in Tyrol, Carinthia, Steiermark, Bohemia, and Moravia, and in the hilly countries of middle and southwestern Germany. Except on the margins of some of its lakes (*e.g.*, Lake Constance and Zurich Lake) Switzerland is also free from it. The disease is endemic only on the humid

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islands of Falster and Laaland in Denmark.   In Sweden it is
to be found on the coast of the Baltic, in the districts of
Carlskrona, Sodermanland and Gestrikland, on the banks of
the river Angermann (62° 20° N. Lat., the most northerly limit
of the disease in Europe) and on the shores of the three
great lakes Wetter, Maeler, and Wener.   The disease is
seldom or never observed in Norway, Iceland, and the Faroe
islands.   It may be found in Russia in the provinces border-
ing on the Baltic, especially in Esthonia, also in Litthao and
in Poland; furthermore, along the marshy banks of great
rivers, such as the Danube, Denieper, Dinester, Don, and
Volga, on the great steppes and on the coasts of the Cas-
pian and Black seas.   Malaria does not appear to prevail
in Scotland and Ireland, and in England it is encountered
but rarely.   It is endemic only on the eastern coast and
in some of the lowlands on the Thames.   The disease in
France is confined principally to the western and southern
portions of the country.   It extends eastward from the mouth
of the Loire as far as Tours and in a southerly direction along
the entire western coast, which abounds in swamps and
meadow lands almost to the Pyrenees.   The southern coast,
as far as the mouth of Rhone, the plain at the junction of the
Saone and Rhone including the city of Lyons and the depart-
ment of Puy-le-dome which abounds in swamps are all well-
known malarial localities.   The most noted home of the malady
in Spain and Portugal is along the south-western coast in the
bottom lands of the rivers.   Still it occurs, often in very
malignant form along the northern coast of Spain, in Galicia
and Austria, in the northern provinces of Portugal, and even
on the uplands of Estremadura and Castile.   In the marshy
valleys and plains of Sardinia and Corsica, and also on the
coasts it is to be encountered.   The most malarious of all
the European countries is, beyond question, Italy.

Aside from the various humid regions in Northern Italy
and that belt of country including the cities of Milan,

Mantua, Pavia, Nice, Venice, and Varona, the entire western coast constitutes a vast hot bed of malaria, which often extends eastwards as far as the foot of the mountains This region begins at Leghorn, and extends through the Tuscan Maremma, the Campagna of Rome, the Pontine marshes, the malarious environs of Naples, and, with the exception of some mountainous regions as far as the southern coast of Calabra. The entire eastern coast, on the contrary, suffers but little from the disease, the only portion affected by malaria being the states formerly in the possession of the Roman pontiffs. The disease is endemic, over large regions and often in a very malignant form in the island of Sicily, the Ionian islands, Greece and Turkey, including Bulgaria, the vicinity of Constantinople, Albania, Roumelia, Moldavia and Wallachia. Regarding Africa, along its western coast, in Senegambia, on the Guinea coast, and on the banks and islands of Gambia, the Niger and the Senegal rivers, malarial fevers flourish to an extent and with a malignity scarcely equalled anywhere else. They also prevail, although in a less virulent form, on the eastern coast, through Mozambique and Zanzibar, as far south as Delagoa Bay, on the greater part of the island of Madagascar, and on the Comoro islands of Anjouan and Mohilla. They are furthermore to be found in Southern Nubia at the Upper Nile Delta, at the junction of the two arms of the Nile, and especially on the banks of Whire Nile, also in Egypt, particularly in Lower Egypt, occurring here, again, on the banks of the Nile and in the moist regions of the Delta ; and also extending along the coast of the Mediterranean sea. In Algiers malaria is very widely diffused and very pernicious, on the southern slopes of the Atlas range of mountains. The disease is also to be found in the interior of Africa in various suitable localities.

So far as America is concerned, it is especially in South America that malaria prevails. The coasts of Columbia and Venezuella, Guiana, the northern part of Brazil, and the

coasts of Ecuador, Peru, and Chilli are extensively malarious. In Central America the Atlantic coast is especially unhealthy, that on the Pacific side presenting only here and there a few circumscribed areas of malaria.

The disease prevails all along the shores of the gulfs of Mexico, and extends up the valley of the Mississipi and along its tributaries. Texas, a part of New Mexico, Florida and Georgia contain malarious regions. Malaria prevails along the coasts of South Carolina, North Carolina, Virginia, and Maryland, but to a lesser degree in the central and northern parts. There is considerable malaria in southern Michigan and along the shores of the lakes Ontario and Erie, less on the shores of Lake Huran, and scarcely any on those of lakes Michigan and Superior. In Pennsylvania and New York there are a few centres of mild malaria. Canada is almost exempt. There is but little malaria, and that of a mild form on the Pacific Coast. The West Indian Islands are very malarious, but the Bahamas the least so.

Regarding India, almost all towns, cities and villages are more or less infested with malaria. But very extensive and malarious regions are to be found in the districts round about the great rivers and their tributaries ; for example, the Ganges in U. P. and the Bengal Provinces ; Ganduck in Tirhoot ; Sarda and Gogra rivers in Oudh ; the Jumna in the Central Province ; the Indus and the Sutlej in the Punjab Province ; the Nurbada in the Bombay Presidency ; the Godaveri in the Madras Presidency ; and the Irravadi in Burma ; all these rivers are annually overflowed by the water of these streams. This is true of the shores of the Brahmaputra and its tributaries likewise, in Eastern Bengal and Assam, which are notoriously known for malarious places, and in these places malaria is very pernicious. There are particularly the cases with regard to the deltas of these rivers, where are the homes for malaria. All along the entire coast of the northern Further India, that is bordering the Hima-

layan ranges called Terai, and higher up in Nepal, malarial fevers flourish to a great extent all the year round with somewhat malignity, not only on the coast, but in the deep and damp valleys of mountainous regions as well. Malaria is prevalent on the marshy banks of small tributaries of the rivers and on the margins of great lakes and hilly regions, in Central India and Rajputana ; in the western coast of India and the low-lying regions of the south coast the disease is not uncommon, while the eastern coast seems to be comparatively exempt.

On the island of Ceylon, however, it prevails with virulence. It is universally prevalent in Further India, especially in Sumatra ; less so in Borneo, Java, and Celebes ; also on the Malacca and the Philippine islands. Malaria prevails in China along the entire southern and southwestern coast, and on the banks of the larger streams with a severity characteristic of the very first malarious regions. It is endemic along the entire coast of Syria along the northern coast of Asia Minor in Arabia ; on the shores of the Red Sea and the Persian Gulf ; along the banks of the river Tigris ; around the Caspian Sea in Persia, and on the elevated plain of Teheran in the most malignant form. Japan has but little malaria and that too in a mild form ; and the coast of the Corean peninsula is only slightly malarious.

So far as Australia is concerned, it appears that malaria may be found on the mainland though in a mild form. Most of the islands of Oceania are almost exempt from malaria, offering in this respect a singular contrast of the lands nearest to them which are so severely affected. There is malaria on the coast of the New Guinea and of the other islands comprised in the Bismark Archipelago. Malaria is unknown in New Zealand and the other islands in Polynesia, as it is also in New Caledonia, though marshy regions abound. It assumes a severe type sometimes on some of

the smaller islands as the New Hebrides and the Society islands and, strangely enough, is entirely unknown on the Sandwich islands and the Samaon islands, as well as in Van Diemen's Land.

CHAPTER III.

ETIOLOGY.

PARASITOLOGY.

It was in the year 1879 that A. Laveran, a surgeon in the French army, serving in the Province of Constantine in Algeria, began to study the pathological anatomy of malaria, and at once directed his attention to the much-discussed question of the origin of the pigment. He observed in the blood of malarial patients certain pigmented bodies different from the *melaniferous* leucocytes ; but he was uncertain as to their nature, until on November 6th, 1880, he discovered that some of these pigmented bodies threw out long *flagella* endowed with such active lashing movements as to convince him, as they have done everyone who has since then seen them, that they are living parasites. Laveran published his observations in a note to the *Achadèmie de Médicine* in Paris, presented November 23rd, 1880. This was followed by the publication of several notes in 1880 and 1881, and in the latter year appeared a small monograph on the parasitic nature of the disease by the same author. He describes in these various early publications: (1) pigmented crescentic and ovoïd bodies ; (2) spherical, transparent bodies, sometimes free, sometimes applied to the surface of the red-blood corpuscle, the smallest about one-sixth of the diameter of a red blood-corpuscle and containing only one or two fine pigment granules, these representing an early stage of development of (3) larger, pigmented, spherical bodies averaging 6mm. in diameter, but sometimes larger than a red blood-corpuscle, and containing numerous often moving, pigment granules ; (4) bodies similar to the last-mentioned, but beset with active motile flagella ; (5) free motile flagella ; and (6) swollen

spherical or deformed bodies, 8—10mm. in diameter, containing pigment, and regarded as cadaveric forms of the spherical parasites.   Laveran noted amœbic movements of the spherical forms, grouping of the small spherical bodies together, and the occurrence of small, colourless, motile bodies, without specific characters, which he suggested may represent perhaps the first phase of development of the parasitic elements.

He regarded all the forms as different stages of development of the same species of organism, and considered the free flagella, which he believed were formed within the spherical bodies and escaped by the rupture of the developing membranæ, as the perfect stage of the development of the parasite and the most characteristic of the same.   To his colleague Richard stationed in Phillipeville, Algiers, Laveran communicated his results.   Richard, in February 1882, published a communication confirming Laveran's observations and adding certain points of importance.   He described the development of the parasite from small, perfectly transparent bodies contained in the otherwise normal red blood corpuscles.   This clear body grows larger, forms pigment out of the hæmoglobin of the enveloping red corpuscle, which thereby becomes gradually decolourised and reduced to a mere colourless shell-like rim, which finally ruptures and sets free the parasites.   This now generally accepted view as to the *intracorpuscular* development of the parasite, which was first announced by Richard, was, however, in the following year abandoned by him in favour of Laveran's view that the parasites develop either freely in the plasma or in close attachment to the surface of red corpuscles or in depressed spots on the surface.   Richard observed spherical bodies with a central *block of black pigment* from which delicate lines radiated so as to produce radiate forms, and noted *amœboid movements* of the parasites.   The first-mentioned observer (Laveran) continued to publish brief communications in 1882 and 1883, and in 1884 he published a

larger work (*Traité des Fivres Palustres*, Paris, 1884) present-
ing his observation and views in detail. In this work he
describes more fully the forms already mentioned, and he
notes the occurrences of *segmented* forms, which he did not
interpret as forms of reproduction, but as forms of degenera-
tion. It is a noteworthy fact that the observations of
Laveran and of Richard were made by microscopical exam-
inations of the fresh blood. In 1883 and 1884 Marchiaf-
ava and Celli published in a number of articles the results
of their studies of stained specimens of dried malarial blood.
With the exception of small, spherical stained bodies in the
red blood corpuscles, which they thought might be *micro-
cocci*, they interpreted the various other stained and usually
pigmented bodies found in the red corpuscles of malarious
patients as probably degenerative changes. As a matter of
fact, the *coccus-like* dots were probably in part Ehrlich's
degenerations, whereas their drawings show that the
supposed degenerative forms were in reality the actual
parasites, which, although not recognised as such, were in
many of their phases actually depicted.

It was in the year 1885 that Councilman, an Abbott, in
the organs from two cases of *pernicious comatose* fever found
and described small pigmented hyaline bodies in and out-
side of red corpuscles, in the capillaries of the brain most
abundantly. Marchiafava and Celli in 1885, as the result of
the examination of the fresh malarial blood came to a
correct interpretation of these bodies, and described them
fully and accurately.

They emphasised especially the amœboid, unpigmented,
transparent intracorpuscular bodies, to which they gave the
inaccurate name of *plasmodia*, which has been widely adop-
ted. They described clearly the intracorpuscular develop-
ment of the parasite, the formation of the pigment out of the
colouring matter of the blood, the consequent changes in
the blood-corpuscles, and they pointed out the probable

reproductive nature of the segmenting bodies, which they
described more fully and accurately than Laveran and
Richard had done. We may here note that Marchiafava
and Celli claim for themselves the discovery of the intra-
corpuscular amœboid forms with and without pigments, and
of the segmented forms, but, as is apparent from the review
of Laveran's and Richard's preceding publications, this
claim cannot be admitted. Marchiafava and Celli, however,
described and interpreted these phases of the parasite
far better than Laveran, and the credit of demonstrating
the intracorpuscular development of the parasite therefore
belongs to them. The publications of these two authors
attracted wider attention than those of Laveran, and from
the year 1885 up to the present time the literature upon the
various questions connected with the *parasitology* of malaria
has constituted a steadily flowing stream. As soon as the
Italian observers had confirmed Laveran's discoveries, there
came similar confirmation from Sternburgh, Councilman,
and Osler (1886-87), and somewhat later by James (1888)
and Dock (1899), in America ; and within a few years
numerous reports from various parts of Europe, Asia, Africa,
and other parts demonstrated the invariable association of
Laveran's parasites with all cases of malarial fever. There
are no observers of any prominence who, with sufficient
opportunity and training for such examination have failed to
recognise the parasites in cases of malaria ; and our accept-
ance of the parasite as the specific cause of the disease has
now no voice of dissent Other observers, following the
fundamental researches of Laveran, Richard, Marchiafava
and Celli (1880—1885), have greatly extended our knowledge
as to many details concerning the structure and life-history
of the parasite and its relation to various types, phenomena,
and lesions of malaria, although not a few important ques-
tions still remain to be settled. The most important of
these later discoveries are due to the demonstration by

Golgi (1885-86) of a definite relation between the cycle of development of the parasite and different stages of malarial fever, and to the recognition by Golgi (1885-1886) of the two varieties of the parasite belonging respectively to *quartan* and *tertian* fever, and by Marchiafava and Celli and Canalis (1889) of the variety or varieties belonging to the æstivo-autumnal fever. These observations have led to two schools of doctrine, the one (and that with the larger number of supporters), headed by Golgi and other Italian writers, upholding the plurality of malarial parasites; the other headed by Laveran, holding the unity of a *pleomorphic* malarial parasite. The first to differentiate the three principal varieties of the malarial parasite in America was Dock (1890—1892); since then a thorough study of the malarial fevers of Baltimore, with careful descriptions of these varieties, has been published by Thayer and Hewetson (op. cit.).

Various observers (especially Celli and Guarnieri, Grassi and Fletti, Romanowsky, Sacharoff, Mannaberg, Antolessi, Bastiamelli and Bignami, and others) have made investigations concerning the intimate structure of the malarial parasites.

After the above historical note we may further emphasise the fact that it is within the red blood corpuscles of many kinds of animals that the malarial parasites of man are developed, and that they are of various species. They have been called *hæmosporodia* by numerous writers; and it is in the red corpuscles of reptiles, amphœba, birds, and mammals that they are known to exist. To account for the natural history of these parasites is a matter of considerable difficulty and complication. Still, if we confine ourselves to the studies of the best known species, namely, the parasites of the warm-blooded animals, we may hold it to be well authenticated facts that they possess two life-cycles; the one being completed in the tissues of an insect, the other within the red cells of the warm-blooded animal. For

instance, the parasites of *Texas fever* (bovine malaria) live in the red cells of cattle; from these they pass into a special kind of tick (*Boophillus bovis*, of Riley), then from the infected mother tick to its progeny, and this by pricking a healthy ox communicates to it the infection. So also with the parasite known as "*protæsoma*," which lives in the blood of birds; from these it passes into the middle intestines of a special kind of mosquito (*Culex pipiens*), where it goes through a whole life-cycle, ending in the salivary glands of the mosquito, and when the latter stings healthy birds, infection of their blood in time occurs.

In the case of human beings, the malarial parasites develop and multiply in the red blood corpuscles of the affected person, where they go through undetermined number of life-cycles, and thence pass into the middle intestines of certain species of mosquito (*Anopheles claviger*), for instance, in which they go through the various phases of a new life-cycle which ends in the poison-salivary glands; from these the parasites pass into man when the mosquito bites in order to obtain nourishment. From this it follows, then, that we have to study two cycles of life in connection with these parasites—one which is completed in man, and the other in some species of mosquito. Though these will in due course be considered in detail, the biological outline of the same may here receive brief mention. The cause of the malarial fever is the phase of life which is completed in man. In this phase the parasites, in their young stage, appear as many small amœboid bodies endowed with more or less rapid *movements* and which exist within the red blood corpuscles, by the substance of which they are nourished, converting the hæmoglobin into black pigment; as they are nourished, they increase in size, and lose a little of their motility, and still within the globules multiply by a process of fission. The daughter cells resulting from this fission become free in the plasma, and

invade other red corpuscles in which latter the same cycle
is commenced again. Intermittent fever and anæmia, the
two salient phenomena of acute malarial infections, are
intimately related to this life-cycle. The first is manifested
when the parasite is undergoing multiplication; the second
is produced principally through the destruction of a large
number of red blood cells, which have gone in part to nourish
the parasites. In all malarial parasites this cycle is com-
pleted essentially in the same manner. The structure is also
fundamentally the same in all; it consists of a vesicular
nucleus furnished with one or more small specks of chromatin,
and by a ring of protoplasm, which, during its development
becomes pigmented by black granulations (melanin),
representing the residua of the digestion of hæmoglobin.
The process of multiplication is identical in all : the chromatin
increases in volume, and is divided into a number of tiny
bodies; thus is formed a varying number of new nuclei,
around which the segmenting protoplasm disposes itself. A
residuum of segmentation, composed principally of black
pigment, is, when the formation of the daughter bodies is
completed, left remaining. Nevertheless, during the time
that the life of these little beings is developing, there are
some differences to be noted in the various malarial parasites,
which increase with the process of development. These
differences, especially in the young forms, relate to the
motility, which may be several degrees ; the minute charac-
ters of the pigment with which the protoplasm is loaded ;
the retrogressive changes undergone by the invaded corpus-
cles ; the length of time necessary for the completion of the
development of the parasite ; the number of daughter bodies
resulting from the division of adult parasite, and certain
points connected with the occurrence of fission. It is a
noteworthy fact that these differences constitute the morpho-
logical basis for the division of the parasite into various
different species, which have constant characteristics, and

do not become transformed into one another. It has from the earliest days been known that malarial fevers present different clinical characters, which permit of their being divided into various clinical groups or species. Recent researches have demonstrated that each of the malarial parasites is the cause of a special kind of malarial fever; so that, simply by examining the blood of a patient, we can authoritatively state the form of the disease from which he is at the time a sufferer.

But, in addition to the life-cycle in question which is completed in man, every kind of malarial parasite has, another, which only begins in man. Some parasitic bodies increase in size without dividing until they form bodies of characteristic shape and structure larger than a red blood corpuscle. These bodies circulate in the blood for several days, without giving rise, when they are alone, to any morbid phenomena. such as fever or anæmia ; then, remaining sterile, they degenerate and disappear. If the blood is subjected for a certain time to examination under the microscope, we shall find that some of these bodies throw out *flagella* which move with great rapidity, and, becoming liberated, move around the red corpuscles with vivacity, whereas others do not present this phenomena. Special bodies, characteristic of one species of malarial parasites, the æstivo-autumnal, called, from their appearance, crescent bodies, represent this phase of life. Numerous investigators have from time to time warmly debated the significance of these bodies. Indeed, it is only comparatively recently, and after a long series of erroneous conclusions, in some of which, however, there was a glimmering of truth, that we have now definitely ascertained that these bodies, first remain in man degenerate and then disappear, are capable of further development when they pass into the intestines of certain species of mosquito ; then starts the second life-cycle— a cycle which can be outlined as follows : When a mosquito

of the right kind bites a sick person in whose blood are the crescent bodies or their homologues in other species of malarial parasites, some of these are taken in with the blood; then in the mid-intestine of the mosquito certain crescent forms give out the so-called *flagella*, which are motile filaments produced with chromatin ; these filaments fecundate other crescent forms, which at this point are capable of penetrating and travelling between the muscular fibres of the mid-intestine. In view of facts, then, it would seem that there is a differentiation of sex in the crescent bodies and their homologues in the other species of malarial parasites. These, becoming *flagellated*, represent—to follow the nomenclature of the zoologists who have described similar phenomena in other *sporozoa*,—the *microgametocytes* (cells producing the male elements), while other *non-flagellated* bodies are *macrogametes*, female element. The fecundated macrogametes undergo their further development between the muscle fibres of the small intestines of the mosquito ; then they are believed to take on a capsule, assume the aspect and characteristics of typical *sporozoa*, and increase progressively in size until they project into the cavity of the *cœlœma ;* at the same time the nucleus divides into a greater number of nuclei which become smaller and smaller, each one of which becomes the nucleus of a *sporozoite.* The latter is a small filament with very slender and usually curved extremities. It has at its centre a little nucleus, which has granules of chromatin, and a few rods. A change now occurs in the capsules of the sporozoa ; they break and become scattered throughout the body cavity. Many of them collect within the cells in some of the tubules of the salivary glands of the mosquito ; and when the insect again stings the human being they are inoculated together with the irating secretion of the gland. This cycle from the small intestine to the salivary gland, is accomplished within a varying length of time from eight to ten days or more,

according to the temperature of the surrounding atmosphere.
According to the species, moreover, of the malarial parasite
there are some slight differences. The parasites pass from
man to the malarial mosquitoes, and from these to man again
with alternating generations. The cycle completed within the
mosquito being characterised by forms of a higher develop-
ment (encapsulated) the malarial mosquito must be considered
a definite lodging place for the parasites; that in man must
be held to be an intermediate abode, as it is characterised by
a lower grade of development—amœboid forms. The whole
of the life of the malarial parasite is not yet fully understood—
at least whether or not this double life-cycle is enough to
ensure the indefinite preservation of the parasites; that is to
say, it is possible for the latter to pass from the infected
mosquito mother to the egg, and thence to the larva and the
new generation of the winged insects, as the parasites of
bovine malaria (Texas fever) pass from the infected tick to
the young generation of ticks. Researches on this subject
are still going on—the more recent of which are held by some
to prove that the two life-cycles in man and mosquito are
sufficient to explain the known facts, and that there does
occur the hereditary infection in the insect in question.

We may here note that several names have been
suggested for the parasite of malaria. Among these may
be mentioned *Oscillaria malariæ* (Laveran), *Plasmodium
malariæ* (Marchiafava and Celli), *Hæmotomonas malariæ*
(Osler), *Hæmotophyllum malariæ* (Metchnikoff), *Hæmamœba
malariæ* (Grassi and Fletti), *Hæmococcidium malaræ* (L.
Pfeffer), *Hæmotozoon malariæ* or *Hæmocytozoon malariæ*
(Osler, etc.,), *Hæmosporidium malariæ* (Danilewsky), of
which names that of *Plasmodium malariæ* has gained wide
currency. There is no reason why it should be perpetuated,
as it is on zoological grounds singularly inappropriate.
There is much to be said in favour of the term *Hæmosporidium
malariæ*, but it has not been generally adopted. Upon the

whole the name *Hæmotozoön malariæ* which expresses nothing as the zoölogical classification of the parasite, and which has been adopted by many writers, may be provisionally accepted until more precise knowledge is reached concerning the zoölogical position of the specific cause of the disease. There is certainly the element of precision in favour of the term Hæmocytozoön.

The unicellular organisms with the physiological characters of animals constitute the class known as the *Protozoa*, and to it the malarial parasite belongs. Bütschli divides the protozoa into orders—*Sarcodinia*, *Mastigophora*, *Sporozoa*, and *Infusoria*. Grassi and Fletti classify the malarial parasite among the Sarcodinia, subdivisions *Rhizopada*, and adopt the name *Hæmamœba malariæ*. Antolessi considers that the parasite belongs to the *Gymnomyxa*, or, more precisely, the *Proteomyxa* of *Ray Lankester*. The great majority of observers classify the malarial parasite among the *sporozoa*, which are divided by Balbiani into the groups *Gregarinidæ Sarcosporidia*, *Myxusporidia*, and *Microsporidia*. Under the *Gregarinidæ* are included the *Coccidia*, with which the malarial parasite is grouped by certain investigators. Under the Gregarinidæ Kruse makes a special family, which he designates as *Hæmogregarinidæ*, and to which he refers the malarial parasite and similar *hæmocytozoa* in lower animals. Labbe gives the name of *Gymnosporidia* to the group the suggestion of which lies in Danilewsky, and termed by the latter *Hæmosporidia*, in which the malarial parasites and similar *hæmotozoa* are arranged by him.

The various ways of studying and demonstrating the malarial parasite will be fully considered under the heading Diagnosis; but we may here note that the examination of thin layers of fresh blood with an oil-immersion lens is the most generally useful procedure. For the study of the finer details of structure the examination of stained specimens

is necessary; and this method   may   be   advantageously
combined with the above-mentioned procedure.

CHAPTER IV.

GENERAL DESCRIPTION.

LIFE-CYCLE OF THE MALARIAL PARASITE IN MAN.

It is now generally agreed that there are several species of malarial parasites, but there is a great difference of opinion as to the number of species of them which may be clearly distinguished, and as to the points of distinction among the same. The malarial parasite is a unicellular, protozoan organism which develops within the red blood corpuscles, and therefore belongs to the group of *Hæmocytozoa*. We shall see later on that organisms closely resembling the malarial parasite have been found in the blood of birds. Our entire knowledge is practically derived from its study in human beings, though numerous attempts to cultivate the parasite artificially have been made. They have, however, been unsuccessful; and the organism has not been satisfactorily determined elsewhere. All the three varieties of parasite have been differentiated, which have characteristics so clearly recognisable that they must be considered as natural species. They are those of the *quartan* fever, those of the *tertian* fever, and those of the *æstivo-autumnal* (or summer autumn) fever. Every one of these corresponds to a determined clinical species of malarial infection. The differences upon which these classifications are based are of various nature: in the first place, there are the morphological differences and those relating to the duration of the cycle of development; in the second place, we have clinical differences in the disease which each of these species produces in man; in the third place, the epidemiological differences, or those relating to the geographical distribution of each species, and the various seasons in which there is a predominance of each

of the *species* in question. Some observers hold that the so-called *æstivo-autumnal* parasites do not constitute a single species, but rather a group of distinct species, though all agree that the tertian and the quartan parasites are distinct.

It may be as well to consider the more important characteristic common to all the varieties of the malarial parasite before dealing with the justification of the above-mentioned division, and the special character of each of the varieties. According to the variety of the malarial parasite, the duration of the cycle of development varies from 24 to 72 hours ; and it also comprises a vegetative and a reproductive stage. It is in the form of small, colourless, amœboid, hyaline bodies, one to two mm. in diameter, that the vegetative phase begins ; and it does so within the red blood corpuscles. We have already seen that Laveran believes that the forms of the parasite which have, since the publications of Marchiafava's and Celli's works, usually been regarded as within the red corpuscles, or attached or applied to the outer surface of the corpuscles. Mannaberg, in 1893, again raised this question by his statement that many of the amœboid forms, particularly in their younger stages of development, are attached to the corpuscles, often in little niches or indentations on the surface.

There is no doubt that the organism may be situated as described by Mannaberg. Marchiafava and Celli who had previously noted this appearance, interpreted it as indicating the extrusion of the parasite from the red blood corpuscle. It is in fact often very difficult to determine with precision whether the organism is on the surface of, or within the, corpuscle ; but the evidence is that the majority of younger forms are intracorpuscular. According to Marchiafava and Bagnami, 1894, the manner of penetration of the youngest forms into the corpuscle is as follows :—" The youngest amœbæ, the offspring of sporulation, by virtue of the vicidity

of their protaplasm adhere to the surface of, and by their movements bury themselves in the contour of the red corpuscles. In this position the parasite attacks the external strata of the corpuscle as a means of nourishment, and after altering these layers is able to penetrate within, and thus become entirely *endoglobular.*" These amœboid forms increase in size, and with the occasional exception of the *œstivo-autumnal* variety, they develop within them a variable number of dark pigment granules, situated, as a rule, near the margin of the parasite. The pigment, which occurs in the form of irregular grains and of fine rods, which may be in active motion within the parasite, increases in amount and in the coarseness of the granules as the organisms continue to develop. The parasite, having attained a certain age of development, which differs as regards the size of the organism in different varieties, gradually ceases its amœboid movements, assumes a spherical or an oval shape, and becomes somewhat sharper in contour. In this condition it may continue for a while to grow. When it has reached its full size—when it may now be called the *full-grown* or *adult* form—it may completely fill the red blood corpuscle or may occupy only a small part of it, these differences depending mainly upon the variety of parasite. The enveloping red blood corpuscle may, coincidentally with these stages of development, undergo various changes, which are of significance in distinguishing the varieties of parasite from each other. The corpuscle may become swollen and pale, or shrunken, or brassy green in colour, or otherwise deformed, or it may appear unaltered in its appearance. In this cycle of development the subsequent changes belong to the reproductive phase. which is shorter in duration than the vegetative. The first evidence of this reproductive phase is the collection of the pigments into a mass of granules or a solid block situated usually at or near the centre, but sometimes near the periphery of the organism. In accordance with the suggestion of Thayer and Hewetson, the term *"pre-segmenting"*

forms—" the *corpicon blocchetto* " of the Italian physicians—
might be used as designation. The process of *segmentation*
begins *coincidentally* with or following this gathering of the
pigment into a clump, sometimes without a definite collection
of the pigment. In its most typical form *segmentation* is
ushered in with the appearance of the delicate lines radiating
from the periphery towards the centre. Eventually the sub-
stance of the spherical organism is divided into a number of
round or oval bodies called *spores*. The enveloping red cor-
puscle, which now may be reduced to a narrow pale rim,
bursts, and the spores are set free ; or the corpuscle may
have disappeared before the process of segmentation is
completed. The pigment remains behind, and is quickly
engulfed by the *phagocytes*. Sometimes in the *æstivo-
autumnal* variety segmentations occur in organism entirely
devoid of pigment. " Sporulating forms" is a term used to
indicate these segmenting bodies. The next thing that happens
is that the free spores speedily invade fresh red blood cor-
puscles, where, as in the small, colourless, amœboid, hyaline
bodies already mentioned, they begin again the cycle of
development. Plehn claims to have observed that the spores
are actively motile and flagellated, but this statement is opposed
to the observations of others. The direct transformation of
the motionless round spores into the small, hyaline, amœboid
bodies has been very rarely observed; but there is no
reason to suppose that between these two forms there exists
any intervening stage. Therefore we can distinguish the
following forms of the parasite in the complete sporulating
cycle of development just described : *Unpigmented, amœboid ,
hyaline bodies ; pigmented, full-grown* or *adult bodies ;
pre-segmenting bodies segmenting* or *sporulating bodies ;* and
spores. We have already seen that, in the æstivo-autumnal
variety, this cycle may be completed without the appearance
of the pigment. These bodies are to be thought of, not as
separate and distinct forms, but simply as successive stages

of development with all transitions from the youngest to the most advanced. Especially can no sharp distinction be drawn between the *unpigmented*-amœboid-hyaline bodies, the *pigmented*-amœboid-hyaline bodies, the full-grown or adult bodies, and the pre-segmenting bodies. The recognition, as a distinct form, of the bodies designated as pre-segmenting is of less practical importance for the *quartan* and *tertian* varieties than from the *æstivo-autumnal.*

To the unpigmented amœboid forms the name "*plasmo-dium*" was originally applied by Marchiafava and Celli. It is frequently employed to designate both the pigmented and the unpigmented amœboid bodies (which may be called, in general, hyaline forms or amœbæ), as well as the parasite in all of its forms. We shall presently see that it is only the *quartan* variety that is found in all its forms with equal frequency in the peripheral circulation and in the blood of internal organs ; whereas segmenting *tertian* parasites are more abundant in the spleen and bone-marrow than in the peripheral vessels, and the *æstivo-autumnal* parasite develops mainly in the internal organs, in the peripheral circulation its segmenting forms being extremely rare. One may also find free in the plasma each of the forms of the parasite which have been described within the red blood corpuscles. They probably escape by rupture of the enveloping corpuscle, a process which one may often witness when examining the fresh blood microscopically. Extra-corpuscular mature forms may possibly segment in the usual way ; but the completion of the cycle of free development in the plasma as regards forms in the earlier stages has never yet been satisfactorily determined. Golgi made a very important discovery, *viz.*, that all of one genera-tion of the parasite form a group, the members of which develop approximately at the same time, and that a definite re-lation exists between the phases of development of the parasite and the stages of malarial fever. The onset of a paroxysm corresponds to the ripening of one generation of the parasite.

A few hours or shortly before the paroxysm segmenting forms appear, and enable the observer to predict the approaching paroxysm. The spores which are set free by the act of sporulation invade the red blood corpuscles and start a fresh generation, which pursues during the paroxysm and the subsequent apyrexia so regular a development that in typical cases the experienced observer can tell approximately by examination of the blood the stage of the disease ; that is to say, the time which has elapsed since the last paroxysm and the time that one may expect the next one. Nevertheless, it is not always the case that the parasite develops with the regularity expressed by Golgi's law ; and especially in the æstivo-autumnal fevers irregularities are very common. The simultaneous occurrence of two or more generations, in different stages of development, may render difficult the interpretation of the phases observed, although even here the observer will be able to draw correct conclusions in *tertian* and *quartan* fevers if he takes sufficient care in procedure. It has not yet been completely proved that there occurs any other cycle of development of the malarial parasite in human beings than that which has been described above, although the possibility of such is by no means negatived. Canalis, in 1889, stated that he believes that he has found evidence that a second, slower cycle of development of the æstivo-autumnal parasite occurs, which is represented in certain of its phases by bodies of the crescentic group to be described subsequently ; and this doctrine, which is opposed by many observers, and does not at present rest upon sufficient evidence, has been accepted by Antolessi and Angelini, Grassi and Fletti, and Sacharoff.

On the basis of clinical evidence, it seems necessary to suppose that the malarial parasite may remain for months in a latent condition in the human body, and then begin to develop again, causing a relapse of the fever. As such relapses may occur in forms of malaria in which crescentic

ıodies do not appear, there must be in these cases some esistant organism other than bodies belonging to the group ıf crescents. We know practically nothing as to the nature ıf these resistant bodies. The hypothesis is advanced by Bignami that they may be *spores* which are enclosed within *'eucocytes* and other *cells*, and which have become surrounded ıy a resistant membrane and have lost their usual affinity 'or the ordinary stains. It is worthy of note that, besides the forms already described as representing phases of the regular sporulating cycle of development of the malarial parasite, there occur other forms which cannot be referred to any cycle of development. These other forms are three in number—*viz.*, (1) *crescentic* bodies and fusiform, oval, and round bodies belonging to the same group; (2) *flagellate* bodies and free *flagella;* and (3) *degenerative* forms. From their size and appearance (which is remarkable) the *crescentic* and *flagellate* bodies are the most *striking* forms of the parasite, and from the beginning have attracted considerable attention. We do not exactly know what is their significance, though sundry theories have been advanced thereon.

Regarding the first-mentioned, the *crescents* develop only from the *æstivo-autumnal* parasites, never from the *tertian* and *quartan* parasites, and will be duly considered in connection with the same. On the other hand, the second-mentioned, the *flagellate* bodies, may form from each variety of the parasite (tertian, quartan or æstivo-autumnal). The weight of the evidence is that they do not exist in the circulating blood, but develop after the blood has been withdrawn from the body, usually within ten or twenty minutes and sometimes earlier. Some observers have found them frequently, others very rarely. They are frequently found if the blood is examined at the right stage of the disease, and time is allowed for their development. Councilman showed that they are more commonly found in the blood *aspirated* by a hypodermic needle from the *spleen* than in

the peripheral blood. They develop in tertian and quartan fevers from the mature, full-grown *extracorpuscular* forms in tertian, especially from the swollen forms larger than the red blood corpuscles. They are therefore found most frequently, a short while before and during the paroxysm. In infections with the *œstivo-autumnal* parasite the flagellate bodies develop from round bodies belonging to the group of crescents, and do not occur in definite relation to the stage of the febrile attack. Flagella are seldom developed by the *intracorpuscular* bodies. There is always pigmentation to be seen in connection with the spherical bodies which become transformed into the flagellate bodies. Marchiafava and Celli state that they once saw an unpigmented flagellate body. These bodies may be somewhat smaller or larger than the red blood corpuscles, the size varying to some extent with the different varieties of the parasite, as we shall presently see. The process of the development of the *flagella* may be studied under the microscope. The pigment granules, which at first (æstivo-autumnal variety) may have been in repose, usually begin to dance about within the organism, often in a lively way. In the æstivo-autumnal variety they usually gather in the central part, but in the others they may be near the periphery or irregularly distributed. The spherical body may acquire an *oscillatory* or *jerking* movement. Projections may be formed and retracted at the periphery, and the whole edge may acquire a vigorous undulating movement. These changes are attributed to the movements of the flagella within the body or in the peripheral layers, and have graphically been compared by Richard to the struggles of an animal to get free. Suddenly, the flagella shoot out from the periphery, and with their active lashing movements produce a violent commotion among the red blood corpuscles and the other small particles which may happen at the time to be in their vicinity. On examining the flagella, closely, we shall observe that they are pale

and thin, presenting often at their extremities and along their course small olive-shaped swellings which may change their position. Here and there a pigment granule is occasionally seen in flagellation. The flagella vary in size, number, and position. Their length may be three or four times the diameter of a red blood corpuscle, or not more than half that size. One to six may be attached to the spherical body. They may project from one side or from any part of the circumference of the body. Their movements may be somewhat rhythmical, they may become slow or even cease, and start up again. Among the red blood corpuscles one may observe free movement of the flagella which have become detached. On account of their pallor, such free flagella would easily be overlooked, were it not for the commotion which they produce among the red blood corpuscles For half-an-hour, or sometimes longer, is usually the duration of movement of the flagella on the slide. The most striking forms of the malarial parasite are these *flagellate bodies;* and the fact of their being a living parasite is at once apparent on examination. It is not surprising that they attracted in an especial manner the attention of Laveran, who, as already mentioned, regarded the flagella as the most *characteristic* and perfect form of development of the parasite.

Subsequent studies have not tended to confirm the conception of Laveran as to their significance. As has already been made clear, the flagellated bodies do not belong to the regular sporulating cycle of development of the malarial parasite in the blood of man. There are various theories as to their significance, of which the following are the most prominent :—(1) They are forms of degeneration, or appearances belonging to the death agony of the parasite. In support of this view, it is urged that the flagellate bodies do not belong to any known cycle of development ; that they are developed only outside of the human body ; that they are

developed from mature forms which are known frequently to undergo undoubted degeneration, such as hydropic swelling, vacuolation, and fragmentation, and which may already show beginning evidences of degeneration; that nuclear substance is absent from the flagella; and that known to zoologists, and interpreted as degenerative, are similar appearances of extrusion of motile filaments in other unicellular organisms. (2) From a study of their structure on stained specimens, Sacharoff believes that the process is degenerative, and that the flagellas are extruded chromatin filaments derived from perverted *karyokinetic* nuclear division. (3) That the flagellated bodies " represent resting states of the organism, capable of existing independently, perhaps even reproducing themselves, but also able, under favourable circumstances, of reproducing the typical growth of the parasite," is suggested by Dock. (4) No less an authority than Mannaberg holds that the flagellate bodies may represent a state belonging to the *saprophytic* existence upon which the mature forms of the parasite enter soon after the blood is withdrawn from the body.

On account of the suitable conditions of environment, they are unable to continue their existence in the blood outside of the body and soon perish. A similar view is advanced by Manson, who suggests that the flagellate bodies represent the first stage, and the detached flagella, in search of their appropriate host represent the second stage of life of the parasite outside the body. Manson (The Golustonian Lectures on the Life-history of the Malarial Germ outside the Human Body) : Brit. Med. Jour., 1896, Mar. 14, 21, 28) lays much emphasis upon the supposed analogies between the malarial germs and of the filaria sanguinis. The correctness or otherwise of this theory will be determined only by future investigations. The same author conjectures that the mosquito is the *extracorporeal* host of the malarial parasite, and the observations of Ross, showing the development of flagel-

late forms in the stomach of mosquitoes fed on malarial blood
are reported by him. For and against each of these theories
there are arguments. In spite of one's natural reluctance
to consider such striking forms as the flagellate bodies as
phases of degeneration, the existing evidence seems upon
the whole in favour of this hypothesis more than in favour
of any other which has been advanced. Still, if Sacharoff's
observations as to the presence of nuclear material in the
flagella be correct, the objection of Grassi and Fletti, that
the flagella are incapable of reproductive development,
because the nucleus of parasite does not divide and enter
them, would be overthrown and the hypothesis of Manna-
berg and Manson would become more probable

Though a term commonly employed, it is evident from
the description of these bodies that the use of the word
flagella to designate the motile filaments, is of doubtful
propriety. Besides the flagellate ones there are various
bodies, often seen in the examination of the malarial blood,
which are undoubtedly degenerative forms of the parasite,
and others which are probably degenerative, although
opinions concerning the latter are divided. The more com-
mon signs of degeneration of the parasite are *vacuolation,
pseudo-gemmation, fragmentation deformities* of shape, parti-
cularly swelling, granular condition of the protoplasm, certain
alterations in the arrangements and appearance of the pigment,
disappearance of nuclear material, defects and irregularities
in staining, and changes in refraction of the organism.
These various degenerative changes produce forms too
numerous to describe in detail. They have often been mis-
interpreted, and described as special forms of the parasite,
some of them as special modes of reproduction, particularly
certain vacuolated and budding forms. In any form of
the parasite degenerations may occur, but they are particu-
larly common in the *extracorpuscular* forms. Mannaberg
describes the disintegration of young *intracorpuscular* forms,

with disappearance of their nuclei. Fragmentations of forms extruded from the blood corpuscles can sometimes be watched before examining fresh blood under the microscope. As a rule, only certain number of mature forms actually enter into reproductive segmentation, and many of the spores or segments perish. If all segmented and the offspring survived, the number of the parasite after a few paroxysms would become enormous. As a matter of fact, degenerations of full-grown parasites are often observed. An interesting form of such degeneration, found most frequently in the mature forms of the tertian variety, is the appearance of swollen, pigmented, so-called hydropic bodies, often much larger than red blood corpuscles, and sometimes containing vacoules. Round bodies simulating spores are sometimes seen in these vacuoles, but on properly stained specimens they are devoid of the nuclear material of genuine spores. Pseudo-gemmation, or appearance of sarcodic buds on the surface of organism, is doubtless a form of degeneration. Such buds may become separated, in the form of hyaline balls, from the parent organism. These evidences of degeneration may appear also in crescents and bodies belonging to this group, and in flagellated bodies. From the latter small hyaline balls, with a flagellum attached, may break off and move around actively. Such bodies look like flagellated spores, but they are not such. Multiplication of the malarial parasite, by budding or simple cell-division, has never yet been satisfactorily established. Although it cannot be denied that other forms of reproduction may exist, the only form of multiplication which has been demonstrated is that of sporulation, also called segmentation, already described. For a time it was the belief of Celli and Guarneri that spherical bodies of the crescentic phase may multiply by the formation of buds (gemmation); but they subsequently abandoned this view, and adopted the new generally-accepted opinion that these budding forms are degenerative. The structure of genuine

spores is absent from these so-called buds. Quinine is capable of producing various interesting changes in the parasite of a degenerative character, which will be described in due course. It is evident that, as the malarial parasite passes its vegetative life, mostly within the red blood corpuscles, it finds its food in this situation. This food may be appropriated both by intussusception and diffusion. Evidence of the former is found in the occasional presence of fragments of corpuscular substance within the body of the amœboid forms. That diffusion is the more important mode of nutrition is doubtlessly true. Many have sought to discover whether the malarial germ may develop in other cells of the body than the red blood corpuscles. Nearly all forms of the parasite have been found enclosed in cells, chiefly leucocytes splenic or medullary cells, and endothelial cells. As such included parasites often present evidences of degeneration, these appearances have been generally interpreted as referable to phagocytic destruction of the parasites, and such they unquestionably generally are. Golgi and Monti have published observations intended to show that the æstivo-autumnal parasite may develop within endothelial and other cells. In the condition in which it exists in the human body, the malarial parasite is very susceptible to injurious agencies. It is quickly killed by the addition of distilled water and of dilute acids and alkalies.

Under ordinary conditions it does not long survive in blood withdrawn from the body. Under certain special circumstances it has been kept apparently alive for two to four days, possibly for a week. Sacharoff observed amœboid movements in the æstivo-autumnal bodies which had been for a week in the intestinal canal of leeches kept on ice ; and he obtained a positive result by inoculating himself with malarial blood obtained and preserved in this way for days in leeches. The *tertian* and *quartan* parasites were

found to be less resistant than the *œstivo-autumnal.* The
parasite does not continue to develop and multiply after
death in the human body. Ripe bodies may segment in
blood outside of the body, but no further development or
multiplication of the parasites has been positively observed
in the various attempts made to preserve and cultivate them.
As to the nature of the parasite in its natural condition
in the outer world no inferences can, of course, be drawn
from these observations. Grassi and Calandraccio have
thought that certain species of amœbæ which they have
observed in malarial districts might be extra-parasitic form.
The failure of artificial cultivations and certain analogies
drawn from the zoological characters of the parasite have
led to the prevalent theory that the malarial parasite passes at
least a part of its existence as a parasite in animal or vege-
table organisms The affirmation as to the mosquito being
a host for the malarial parasite has already been mentioned.
Though malaria can be transmitted by inoculating into
healthy individuals, either subcutaneously or intravenously,
blood from a malarial patient, there is no evidence that the
malarial parasite is eliminated from the human body in a
condition capable of infecting another individual or the
locality. That the germ is capable of entering upon resistant
phase of development seems highly probable in view of the
evidence that malarial fever can be contracted from tha air.

CHAPTER V.

THE MALARIAL PARASITE.

Concerning the nature of the malarial parasite much controversy has raged in the past. We have already seen that there are two schools of opinion as to this : the one led by Laveran holding that the malarial parasite is a single species with *pleomorphic* characters, the other believing that there are three or more species, or at least varieties, of the malarial parasites. Investigations in malarial regions have supported the latter theory, which originated with the Italians. In 1885 and 1886, Golgi first differentiated the parasite of quartan fever than that of tertian fever ; and Marchiafava and Celli and Canalis, in 1889 and 1890, differentiated the variety of the parasite characteristic of æstivo-autumnal fever. The credit of having first discovered the æstivo-autumnal parasite has been warmly contested by Canalis on the one hand, and Marchiafava on the other. The differentiation of this parasite was not made all at once, and with the same precision in all details, as in the case of Golgi, sharp separation of the quartan and tertian parasites. From the beginning of his researches, Golgi suggested (1885-86) that the crescentic bodies belong to a special cycle of existence different from that of the tertian and quartan organisms, and noted their occurrence in irregular malarial fevers. Councilman, in 1887, emphasised the association of crescents with remittent fevers and malarial *cachexia*. In February 1889, Golgi definitely expressed the opinion that, in addition to the malarial fevers caused by the quartan and the tertian parasites, we must recognise another type of fever associated with unpigmented amœboid forms and crescents. There appeared, on September 13th, 1889, a preliminary communication of Marchiafava and Celli,

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which must be regarded as furnishing the first clear and sharp description of the essential differential characters of the æstivo-autumnal parasite, with especial emphasis on the occurrence of unpigmented organism.

In October 10th, 1889, appeared the preliminary communication of Canalis, in which likewise the essential characters of this parasite were described ; and a greater emphasis was laid upon its relation to the crescents than had been done by the two authors just mentioned. There is much difference as to the number of the æstivo-autumnal parasites. All the adherents of the doctrine of plurality agree that there are at least three varieties of malarial parasites, *viz* , the *quartan*, the *tertian*, and the *æstivo-autumnal*, distinguished from each other by morphological and biological characters to be subsequently described. Though there remain many unsolved problems for the future to clear up, the discovery by Golgi of the definite cycle of development of the malarial parasite and the recognition of several distinct varieties have done much to bring order out of the earlier chaotic condition, when a multitude of parasitic bodies were described without knowledge of their significance or mutual relations. That all the so-called varieties of the parasite may be explained simply as phases of a single pleomorphic organism, influenced by various conditions of environment, such as locality, season, individual predisposition, and various unknown circumstances, is an hypothesis urged by Laveran in opposition to the doctrine of plurality. He contends that the characters upon which a division into separate varieties is based are insufficient for such a purpose and inconstant ; that one so-called variety under certain conditions may be transformed into another ; and that there is no definite necessary relation between the types of fever, such as quartan, tertian, quotidian, irregular, continued, and the form of the parasite present.

He argues that the doctrine of plurality is not supported by the experimental production of malaria by inoculation ;

and he emphasises the view that malaria, with all its diverse
manifestations, is, nevertheless, clinically and anatomically
one disease, and has always been so regarded. He thinks,
also, that the variations of the malarial parasite can be
explained in a large part by the varying rapidity of develop-
ment. Now, when we come to consider the force of these objec-
tions of Laveran's, it must be admitted that, as we are unable
to cultivate the malarial parasite artificially, and are ignorant
of its life-history and the conditions of its existence outside
the human body for the most part, the possibility must be
admitted that under certain conditions, at present not fully
understood, one variety may be transformed into another.
But, on the other hand, the existing evidence (and it is
already considerable) goes to show that under the conditions
which we can at present control and study, each of the three
principal varieties of the parasite preserves its identity and
is not transformed into another variety, *e.g.*, the quartan
and the tertian, or either of them into the æstivo-autumnal.

There are various arguments in favour of the doctrine
of plurality, of which the following are, in brief, the
principal :—

(1) Each well-established variety of parasite presents
morphological and biological characters which
are sufficient to identify it.

(2) They each correspond to definite types of fever.
Genuine quartan fever can be produced only
by the quartan parasite. As will be explained
in the clinical part of this book, other types of
fever may be caused by more than one variety
of parasite, and much complexity may result
from multiple and mixed infections and vari-
ous irregularities ; but the recognition of cer-
tain fundamental types of fever, characteristic
of each variety of the parasite, is not presented
by this.

(3) Grassi and Fletti, and Calandraccio have carefully studied, for weeks and months, cases of pure infection with one variety of parasite without any indication of the transformation of one variety into another. One cannot interpret in favour of the metamorphosis of one variety into another the appearance of a second variety of parasite in localities where there is opportunity for renewed infection.

(4) One encounters only one or two varieties of the parasite in certain localities. In a few places only the quartan, or more frequently only the tertian parasite is observed ; in most places where malaria is mild and infrequent, only tertian and occasionally quartan parasites, with entire absence of æstivo-autumnal parasites, are found.

(5) The experimental production of malaria furnishes strong arguments in favour of the constancy of the varieties of the malarial parasite. In 1882 and 1883, Garhardt was the first to produce malaria experimentally by the subcutaneous injection of blood obtained from malarial patients. At this time the malarial organism was not generally recognised. Since these first experiments similar ones have been repeated, usually in the manner of intravenous injections of malarial blood, with positive result in a large number of cases. The experiments before 1889 were made without determination of the exact variety of the parasite injected and found in the experimental case. In 1889, Gualdi and Antolessi, without full knowledge of the critical nature of the experiment, injected two patients intravenously

with 3 *c.c.* of blood from a patient suffering from quartan fever and possessing quartan parasites. In each of the inoculated individuals irregular fever with æstivo-autumnal parasites developed. These two cases are constantly adduced as a main support of the doctrine of mutability of the varieties of the parasite, but unjustly so, for it was subsequently determined that the patient from whom the blood was obtained had previously suffered from irregular fever, and he subsequently developed characteristic æstivo-autumnal organisms; so that the experimenters themselves have expressed the opinion that at the time of the inoculation the patient furnishing the blood had combined quartan and æstivo-autumnal organism, the latter being overlooked In view of the uniform results yielded by the numerous subsequent experiments in support of the doctrine of immutability of the varieties of the parasite, there can be little doubt that this latter opinion of Gualdi and Antolessi is correct. It has been found regularly since these experiments, that if the blood containing only the quartan or the æstivo-autumnal parasite be injected intravenously into a person unaffected with malaria, the variety of the parasite injected, and only that variety, appears in the blood of the experimental case. When the two varieties of parasite are injected, or when the malarial blood is injected into a patient affected already with a malarial organism other than that injected, then it usually happens that one variety supplants the other, most frequently the one injected supplanting

that already existing in the individual subjected to inoculation. The numerous inoculation experiments, showing the identity of the parasite in the experimental case with that in the blood used for injection, furnish the strongest arguments in favour of the malarial parasites being more than one only.

CHAPTER VI.

CLASSIFICATION OF MALARIAL PARASITE.

The parasites of malaria have been classified in various ways, some observers placing them amongst the *Rhizopoda*, others regarding them as *Sporozoa*. For various reasons, Golgi classed them with the Rhizopoda in his earlier researches; but chiefly because he thought it certain that these parasites multiplied in the free state, whereas the sporozoa never did. They appear as typical sporozoa in the mosquito. Labbe, Metchinikoff, and Danilewsky are amongst those who maintain that these parasites belong to the class of sporozoa; and the classification has apparently found a firm support from more recent researches into the life-cycle of the parasite outside the man. The *protozoa* lead a parasitic existence and multiply by sporulation. The *sporozoa* are such; and this class has been divided into various orders and sub-classes, *e g.*, *Gregarinidea*, *Coccididia*, *Myxosporidia*, *Sarcocystidia*, *Microsporidia*, to which Mingazzini has proposed the addition of the sub-class *Hæmosporidia*. All the parasites that are found in mammals, reptiles, frogs, and birds are included in the latter. Labbe divides the parasites of the blood into two orders which he classes under the *sporozoa*, the *gymnosporidia* (including the parasites of man, which he calls *Hæmamœba* Laverani), and the *Hæmosporidia*. *Plasmodium* (parasites of man), *Hæmogregarina* (*Drepanidum* parasites of the frog), and *Hæmoproteus* (parasites of birds), are the three different genera under which Celli, Kruse, and Sabfelice group all species. On the other hand, two genera are recognised by Grassi and Fletti to comprise the malarial parasites and the forms related to them : (1) The genus *Hæmamœba*, which includes the following species· *Hæmamœba malariœ* (quartan parasites), *Hæmamœba vivax*

(tertian parasites), *Hæmamœba præcox* (pernicious parasites), and *Hæmamœba immaculata* (pernicious). To these may be added another group of species, which are the parasites of birds: the *hæmamœba relicta* (in the sparrow, lark, etc.), the *subimmaculata* (in the hawk), and the *subpræcox* (in the lark, owl, etc.). (2) The genus Laverania, to which belongs a species that lives in man, *Laverania malariæ* (crescent parasites); and other parasitic species in other animals, *e.g.*, *Laverania ranarum* (in the edible frog), and the *Laverania Danilewsky* (in many pigeons, sparrows and birds of prey). As already mentioned, Laveran is among the few to hold that the parasite of man is a form of species which is polymorphus— one species with variable developments. The various febrile types, he thinks, are not due to differences in the parasite, but, as yet unknown, to a disposition on the part of the affected organism: in fact, he states that there are many cases of fever in which there is no constant relation between the febrile type and the parasitic form. This last statement of Laveran is contradicted by all modern researches ; and the view held in general by the Italian observers, who, following Golgi, distinguished various species of malarial parasites, in intimate relation with the variety of the febrile seizure, may be adduced in opposition to that distinguished investigator's opinion. According to whether or not there is a formation of *syzygies*, Mannaberg divides the parasite into two groups :—

    (1) parasites with sporulation without *syzygies*, *i.e.*, parasites without crescentic forms : the same to include the tertian and the quartan forms of the disease.

    (2) parasites with sporulation and with the formation of *syzygies* (crescents) ; the same to include the malignant tertian parasite, the pigmented quotidian parasite, and the non-pigmented quotidian. It is worthy of note that, as regards

· the fundamental basis of this classification, it is not possible to contrast the æstivo-autumnal parasites (Mannaberg's second group) with those of the tertian and quartan; by reason of the presence or absence of crescent bodies. Indeed, it has now been demonstrated that in the tertian, for instance, there are parasitic forms, large *mononucleated* pigmented bodies, which have the same biological significance, and the same ulterior development, as the crescent forms. As to the subdivision of the second group, it is held that there is not as yet sufficient proof to allow of the admission that the parasites which complete their entire cycle without becoming pigmented, represent a species by themselves, although the probabilities point that way. In spite of the distinction of the æstivo-autumnal parasites, into quartan parasites, and parasites of the malignant tertian, these two forms are not looked upon as distinct species, but as closely related varieties of the æstivo-autumnal parasites. By classifying the malarial parasite into the three species of æstivo-autumnal, tertian, and quartan parasites, we take into consideration only the best proved facts, leaving out all disputed points ; so that, if we examine the classifications proposed by the various authors, we find that, in spite of divergencies, they all agree in considering three species as distinct. It is likely that the first includes several closely related varieties.

We find that there are three arguments upon which the division of the malarial parasite into the above-mentioned species rests, *via* :—

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(1) In all essential morphological and biological characteristics the three species exhibit perfect constancy, which same have been noted everywhere, where malarial fever abounds, so that they can easily be recognised on examination under the microscope.

(2) A determined clinical species holds an indisputable and close relation to them.

(3) They are capable of being inoculated from man to man; and without ever being transformed into another, each reproduces its own form. A fact of scientific importance and of great practical value is constituted by the constancy of the morphological characteristics, because it permits us to make with positiveness the differential diagnosis between the three species of parasites described: from a prognostic point of view, also, a fact of no inconsiderable importance. Both morphological and biological are the differences between the quartan and the tertian parasites, so that the two can easily be distinguished by a capable investigator. Indeed, the differences are four in number, *viz.*,—

(*a*) Differences in the developmental cycle, the ordinary tertian parasite completing its whole life-cycle in two days, one day more than that being necessary for the quartan to do so.

(*b*) Differences in the character of the amoeboid movements, the quartan having less active movements than the endoglobular amoeboid forms.

(*c*) Differences in the behaviour of the parasite towards the substance of the red blood corpuscles, the tertian parasite discolouring the red cell

much more rapidly than the quartan and more decidedly. Furthermore, the cells invaded by the tertian parasite become swollen and perhaps tend to become smaller, whereas those invaded by the quartan either preserve their normal size, or tend to become smaller, than the red corpuscles.

(d) Differences in the morphological characters, the pigment granulations of the tertian are extremely fine ; those of the quartan hæmamœba are larger. The quartan parasites have better defined and clearer outlines than the tertian. There are some differences to be found in the sporulating forms. These consist in the number of bodies resulting from fission, *gymnospores*, which average 15 to 20 in the tertian parasites, 6 to 12 in the quartan ; and in the size of individual bodies, which is larger in the quartan. Moreover, within each spore resulting from the segmentation of the quartan amœba, we see a central shining sphere, which represents the so-called *nucleus* or *nucleoliform* body, but in the tertian gymnospore this is not of constant occurrence. The differential diagnosis between the parasites of ordinary tertian and that of the *æstivo-autumnal tertian* is always easy ; for the differences which same relate to the size of the parasite, and the appearance of the parasitic forms are very marked. Now, regarding the size of the parasite, the parasites of æstivo-autumnal tertian, at the same stage of development, are always larger than those of the ordinary tertian appear to be. So far as the appearance of the parasitic forms is concerned, the *æstival*

parasites, in their first phase of life, long
preserve the property of taking on the charac-
teristic annular form in fresh preparations ;
similar rings are seen in the ordinary tertian
but rarely, and they are never seen at an
advanced stage of development. Moreover, the
annular and discoid forms of the æstivo-
autumnal parasite have more distinct outlines,
and stand out more conspicuously against the
background of the red blood corpuscle than
the corresponding forms of ordinary tertian do.
It should also be noted that there are four other
differences worthy of consideration ; and these
are the characteristics of the pigment, the
alterations produced in the invaded red blood
corpuscles, fission forms, and the forms which
begin in man the life-cycle which is continued
in the mosquito. In the ordinary tertian the
pigment is abundant and nearly always motile ;
it is in very fine granules, rarely immotile, and
arranged for the most part upon the extreme
margin of the amœboid body in the parasites
of the *æstival* tertian. When the red blood
corpuscles are invaded, they swell with great
rapidity in the ordinary tertian ; while they
tend to become smaller and to shrivel, the colour
of the hæmoglobin becoming deeper than
under ordinary circumstances in the æstival
tertian. Fission is accomplished by similar
process in the two forms of tertian ; but the
completely sporulated forms are usually much
larger in the ordinary tertian, and the
individual *gymnospores* are larger than the
parasites of the *æstival.* The forms which
begin in man the life-cycle which is con-

tinued in the mosquito, are represented in the ordinary tertian by the large, round, pigmented bodies mentioned above ; whereas in the æstivo-autumnal parasites—æstival tertian—they are represented by the characteristic crescents. Furthermore, the *flagellated* bodies of simple tertian usually possess a larger number of *flagella* than those of crescent origin exhibits ; and, finally, it may be noted that there are other differences relating to some biological properties, *e.g.*, the pathogenic action on man, and the distribution of the parasitic forms in the circulation. We may safely affirm that at the present time no doubt can be cast upon the possibility of distinguishing these three species by microscopical examination of them alone ; for the differences between the tertian, the æstivo-autumnal and the quartan parasites have, since the studies pursued in Italy, been recognised by nearly all investigators who have taken up the subject. The establishment of the opinion that we are dealing with distinct species, not intransferable, has been greatly contributed to by the results of the injection of the malarial blood in man. These experiments show that when blood containing one kind of parasite only—as, for instance, the quartan or the tertian, is injected under the skin or into the veins of a healthy person, parasites identical with those injected will be developed, and a fever, similar to that in the person from whom the blood was taken, will be caused. We find that, among all the inoculation experiments which have been made, only to appear at first sight to be opposed to

the theory of distinct species. These relate to two patients of Gualdi and Antolisei, in whom they injected blood with quartan parasites, with the result that one of the patients developed a fever with æstivo-autumnal, and the other with tertian parasites. Still, one may call in question the statement that only two experiments furnish valid arguments in support of the belief that the parasitic forms of quartan can be transformed into *æstival* or *tertian* forms. Antolessi gives a critical review of these two cases, in which he states that the patients from whom the blood for experiment was taken had in the last few months suffered from fevers of various types — quartan, tertian, quotidian, and irregular. Therefore, it is evident that in the blood of these patients there co-existed the germs of three species of malaria, but in varying quantity; so that the existence of mixed infection had escaped the notice of the observers, and they supposed that they were using the blood of a person with pure quartan for the inoculation. Indeed, the same observers always obtained the reproduction of the same form in the person inoculated, in subsequent experiments in which they used the blood of patients with a recent and pure infection. The majority of recent investigators have recognised the intimate relation between the three parasitic species and the clinical forms of malaria. Each species of malarial parasite differs from the others in respect to the pathogenic action upon man, as a study of the various species of malaria will show. Much is made of the fact, by the supporters

of the doctrine of polymorphism, that it is not
infrequent to see the same patient affected by
different types of fever with different species
of parasite. But this merely proves that the
parasites and the various febrile types can
succeed each other alternately in the same
patient, and does not in the least demonstrate
that they are transformed into one another.
Facts such as these only prove that, in mixed
infections given by two species of malarial
parasite, the two infections tend rather to
succeed each other than to co-exist. This is
shown by several interesting experiments of Di
Mattei, who, having inoculated quartan para-
sites into a patient who had crescent forms in
his blood, saw the crescent infection disappear
and the quartan develop; and, on the other
hand, he saw an æstival infection develop
and the quartan disappear upon inoculating,
with semilunar blood, a quartan patient. We
must also remember, with the view to explain
the succession of febrile types and of the various
parasites in the same person, that mixed infec-
tion due to two kinds of parasite may co-exist,
while only one of them exhibits characteristic
clinical manifestations. For instance, we fre-
quently see patients with æstival tertian who
have tertian parasites in the blood in addition
to the æstivo-autumnal parasites. In spite of
this, the grave clinical forms of æstival tertian
keeps the first place, and interferes with a
recognition of the mixed infection, unless the
blood be examined. But, as a rule, the tertian
parasites disappear very soon from the circu-
lating blood, and the æstival affection is to all

appearances pure; this does not prevent the
occurrence of an ordinary tertian in its typical
form and with characteristic parasites in the
relapses after several months' interval. This
fact has been adduced in support of the idea
that the æstival parasites could be transformed
into the tertian, with a corresponding trans-
formation of the febrile type. But the fact
that the infection was a mixed one from the
beginning, and that during its course the para-
sites alternated, each one causing its own
special type of fever, will be demonstrated
on accurate observation. Therefore, the ap-
parent transformation of the febrile type may
be due to the fact that in a mixed infection
one of the parasitic species may remain latent
for a long while, and then, from some cause or
other, may re-appear with its characteristic
febrile type. The view that all the malarial
parasites are divided into determined species
that are not transformable is also favoured by
the other facts taught by clinical experience,
the geographical distribution of the various
kinds of fever, the almost exclusive domination
of one species in certain localities, etc. The
specific nature of the tertian, quartan, and the
æstivo-autumnal parasites are the arguments
which have already been briefly outlined as
demonstrative of our contention. But, while
those of the tertian and the quartan each
represents a species which, wherever tertian or
quartan fever exists, occurs with certain deter-
mined morphological and biological properties,
whether the same is the case with the æstivo-
autumnal parasite is a question, *i.e.*, we must

enquire if the parasite we have described as æstivo-autumnal represents one individual species, or if they include various species and varieties. The question is still, however, an open one. Considering that in the groups of fevers bound to the biology of this parasite, there are two fundamental clinical types, *viz.*, the æstivo-autumnal tertian, which is the predominant and most important, and the quotidian ; we must endeavour to ascertain morphological and biological differences which exist between the parasitic forms found in cases of typical æstivo-autumnal tertian, and those which in cases of quotidian are to be observed.

The morphological and biological differences in question relate to five points, *viz.*,—

(1) the duration of the cycle of development,

(2) the pigmentation,

(3) the size of the parasite,

(4) the amœboid movements, and

(5) the duration of the various life-phases in relation to the febrile cycle.

Let us consider these briefly. The duration of cycle of development, which in the quotidian is completed in about 24 hours, in the tertian is completed in 48 hours, according to the most modern researches. In adult forms of tertian the pigmentation is more abundant, and sometimes endowed with oscillatory movements, which in the quotidian is never observed. The size of the parasite at the same stage of development is greater in the tertian parasites than in the quotidian ; in the former even the fission forms are of greater dimensions. In the tertian the motility is preserved for a longer time ; even in the pigmented adult bodies the movements are very active, and the amœba tends to assume

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various grotesque shapes from the rapid emission and retraction of the pseudopodia.

The movements in the pigmented stage are less active, and of shorter duration, in the case of the small amœba of the quotidian. Regarding the last-mentioned point, the duration of the various life-phases in relation to the febrile cycle, the duration of the non-pigmented amœboid form is very long, and may even go beyond 24 hours. Moreover, the forms of the young generation in summer tertian usually appear in the blood several hours after the beginning of the attack, much later than those of the quotidian, to put it differently. The resemblances, in spite of these differences, are so great as to render a differential diagnosis very difficult ; all these parasites affect the red blood cells in the same way, all possess a life-phase represented by the crescent forms. Therefore, one may reasonably enquire if these parasitic varieties are such in the true sense of the word, or if it is one parasite which exhibits great variability in the duration of its development, so that between the two extremes (24 hours in the quotidian, and 48 hours in the tertian) these are all in the intermediate grades. It would be easy enough to ascribe the morphological differences to the varied duration of the life-cycles if we were to hold this view. The *hæmamœba immaculata*, the parasite which completes its whole life-cycle without becoming pigmented, probably represents a species or variety by itself of the æstivo-autumnal parasites. But, in the present state of our know-ledge, the question cannot be definitely answered in relation to these parasites. Recent facts learnt in investigation of the life-cycle of the malarial parasites in mosquitoes give support to the opinion that malarial parasites represent distinct species. These researches permit us to dwell upon the question of the difference of species only with reference to the æstivo-autumnal and the ordinary tertian parasites ; for observations are as yet incomplete with regard to the life

of the quartan organism. According to Bignami and Bastianelli, the tertian sporozoon in the anophelic life is to be distinguished from those of crescent origin by the morphological characters, hereafter to be given ; the young bodies chiefly distinguished by the form of the sporozoa and the character of the pigment ; the forms undergoing development by the size of the little bodies successively produced by the division occurring in the nucleus. In general, the size and disposition of the so-called residua of segmentation will serve for distinction of the adult forms with sporozoites. These facts are borne out by the studies of various observers. Indeed, if we nourish mosquitoes with blood containing crescents, and after these have completed their whole life-cycle up to the infection of the salivary glands, with sporozoites, and cause the same mosquitoes to bite a person who is healthy, an æstivo-autumnal fever will develop. This experiment has been made by the two authors mentioned above, in the winter—a season in which the anopheles taken in a free state did not give æstival fevers, but when they produced fever at all, caused the ordinary tertian. They both affirm that in the mosquito the distinction between the species of malarial parasite does not undergo any change.

We shall now consider in detail each of the varieties of the malarial parasite.

CHAPTER VII.

In the majority of malarial regions these are the rarest forms of the malarial parasite; but there are certain places where it (quartan fever) is the prevailing variety. Being particularly common in the neighbourhood of Pavia (Italy), the quartan parasite was the first to be differentiated and described by Golgi (1885-1886). In the case of the quartan parasite there are two life-cycles to be distinguished—one being completed in man, the other begun in man and completed in certain mosquitoes.

The bodies of the first cycle are well known from Golgi's description (Arch. per li Sci Med., 1886); those of the second cycle are not so generally known as the corresponding one of the tertian and æstivo-autumnal germs. The life-cycle, which is completed in man, develops in a period of three days, i e., in the interval between two typical quartan attacks, and is intimately and regularly related to the occurrence of these attacks; in fact, the onset of a febrile attack coincides with the stage of multiplication of parasites. The whole development of parasite up to sporulation may be easily followed in fresh preparations during a quartan attack, and during the two days of apyrexia between this and the next attack. No phase of life escapes the observer, because development occurs in the circulating blood; while in the case of the æstivo-autumnal parasites the adult and multiplying forms accumulate in the internal viscera, and even the tertian parasites show a tendency to accumulate at the same stage in the vascular area of the spleen, although not to such an extent as to prevent in the peripheral blood their entire development being followed. Less motile in character and less transparent in appearance are the young parasites,

which occur as small endoglobular amœboid bodies without
pigment, exactly similar to the tertian bodies for the
distinction named. They appear in the blood during the
febrile attack, and rapidly become pigmented, so much so,
that on the first day of apyrexia we find in the blood
endoglobular pigmented parasites, about one-fifth or even
one-quarter the size of the red blood corpuscle, and endowed
with torpid movements, as shown by the slow change in the
shape of their outlines. The red cells containing them are
normal in size and appearance. During the whole period
of apyrexia the parasites increase slowly in size, preserving
the same appearance; their movements become gradually
slower, so that they do not tend to assume the irregular
and grotesque shapes taken by the tertian parasites, but
retain more or less round. As the parasite grows the
pigment becomes more abundant, and occurs in black granules,
which are notably larger than in the tertian parasites, and
usually non-motile. The red cell preserves its normal size, or,
if modified at all, tends to be somewhat smaller; its substance
is gradually replaced by the parasitic body which is deve-
loped within it; but around the latter there persists, up to
the point of complete development, a sort of ring or substance
coloured by hæmoglobin : indeed, even darker than normal
may be the hæmoglobin colouration of the residual portion of
the red blood corpuscle. On the other hand, the adult forms
are round pigmented bodies, almost as large as a red blood
corpuscle, which have invaded the whole (nearly) of the
containing corpuscle, of which only a slender zone around
the parasite still persists. We see others along with these
forms in which there is apparently no trace of the red blood
corpuscle but representing the residuum (peripheral) of the
invaded cell, a very thin involucrum will be discovered on
closer examination. From 8 to 12 hours before the febrile
attack, whose onset corresponds with the end of their life-
cycle, these bodies, which have attained the maximum growth

of quartan parasites, and in whom we can see the first
indications of the internal changes which lead to fission
or sporulation, are found in the blood. In the course
of 8 to 12 hours, and in fresh specimens, some of the
phases of segmentation may also be followed, and are the
first stages of the process; on the other hand, we find that
nuclear division begins first in the adult pigmented bodies,
with irregularly disseminated pigment in the case of pre-
parations properly stained. What happens in fresh pre-
paration, is that in the adult forms the pigment tends gradu-
ally to accumulate in the centre, where from the beginning we
find the pigment irregularly arranged in striæ or trabeculæ, or
sometimes in striæ radiating from the centre to the periphery
of the parasitic body ; then the pigment which forms the
striæ gradually gathers towards the centre forming a globular
mass with well-marked outlines.

At the same time the parasitic body shows a line of
division, which becomes little by little more distinctly visible.
The formation from 9 to 12 pyriform or ovoid bodies, which
arrange themselves around the central mass of pigment with
remarkable regularity, is the result of all this and the final
one. Continuing to observe under the microscope one of
those segmented forms, we often see the small pyriform or
oval bodies, which have arranged themselves in wreath
form, take on a more globular appearance, become slightly
displaced and pushed away from each other ; and then, when
the thin *involucrum* formed by the red blood corpuscle has
disappeared, they appear simply as little masses of free,
rounded bodies near the residual block of pigment, their
original regularity of arrangement being lost. The sporula-
tion is broken up at this point, and new red blood corpuscles
in which they begin their regular life-cycle are invaded by
the individual gymnospores. The same regularity is not
always seen in connection with the occurrence of sporulation,
more especially in relation to the deposition of the pigment,

which may collect in two or more masses, or remain in an irregular fashion between the bodies resulting from fission, instead of being centrally or subcentrally situated in one mass. But these details are of no importance. Of more interest, however, is the fact that sporulation may occur in bodies which have not attained the size of normal adult parasites, but which are decidedly smaller than the corpuscles containing them, of which as much as a third may persist   In the other species of parasites, the size of the adult bodies in segmentation may vary between wide limits. In this respect, indeed, the quartan parasites show more regularity than do others. The quartan parasites correspond in structure with those of other species. The young and the developing forms have a pigmented cytoplasm, and a nuclear formation consisting of a little body of chromatin surrounded by a pallid zone. The line of demarcation between a clear zone—nuclear juice—and the cytoplasm is very distinct.   In the advanced stage of development the chromatin, instead of being gathered into one deeply-stained body, is arranged in *rods* and *filaments*. The segmentation of the nuclear chromatin, by which the nucleus divides into two, four, etc., occurs in the same way as in the connection with the tertian parasites, in bodies in which we witness the splitting up of a mass of chromatin into two parts, we see the mass assuming irregular and dentilated outlines, showing probably that it is made up of small filaments of chromatin. Around the individual masses of chromatin, resulting from the successive divisions, the pallid zone is always visible, although it is thinner and has less distinct outlines than in the younger forms. The individual gymnospores are composed of a cytoplasm which stains a deep blue, and of a small concentrically situated body of chromatin (corresponding to the shining spot seen in the spore in fresh preparation) of compact appearance, but without recognisable structure. This structure, in all the essential points, is the same as that of the

quartan parasites. According to Grassi and Fletti, the young quartan parasites which have just entered into a red corpuscle, consist of a relatively large, eccentric nucleus, surrounded by a scanty cytoplasm, and furnished with a delicate membrane, containing the nuclear juice and the so-called nucleoliform node, which represents the chromatin substance of the nucleus and lies close to the nuclear membrane. The cytoplasm may possess an alveolar structure. With the development of the parasite the cytoplasm grows more than does the nucleus; and when the hœmamœba has reached a certain size, we often note the appearance of filaments which unite the nucleoliform node to the nuclear membrane; the node and the filaments represent the so-called nuclear reticulum. Later, the nucleoli form node increases in size, and then divides into four, five, eight, or ten little nodes, each of which becomes surrounded by nuclear juice and a very delicate membrane. What becomes of the reticulum and nuclear membrane during multiplications, the authors quoted above have not been able to ascertain. The amœba thus becomes multinuclear. Later on the process is held to indicate that the hæmamœba is reproduced by direct division of the nucleus, a little cytoplasm forms around each nucleus, and thus is formed the complete gymnospore. Nevertheless, it would appear that multiplication occurs by a rudimentary form of *karyokinesis*, not by the direct division of the nucleus; and, furthermore, we do not see the nuclear membrane, whose presence can at the most be merely deducted from the distant line of separation of the clear zone from the cytoplasm, nor we do see the nuclear reticulum from the nucleoliform node, etc. Now regarding the forms which begin in man, the cycle has completed in the mosquito, as is also the case with the cycle of the quartan parasite in that insect, these are but little understood. We can see adult forms, which take up nearly the whole of the substance

of the red blood corpuscle, which have irregularly disseminated pigment and abundant nuclear chromatin arranged in threads or rods. As in these forms, no matter how large they grow, we see no sign of division of the nucleus, while in bodies of equal size which end in sporulation the nuclear division is already well advanced that they remain sterile in man, and are analogous to the large pigmented tertian forms which are also sterile in man, is a natural supposition. These adult bodies, undergoing degenerative processes similar to those of the tertian, are to be seen in fresh preparations. It is a well-established fact that the quartan parasites may give rise to flagellated forms ; yet, according to the experience of many, it is rare to find this phase of life. While the patient investigation of a case of æstival or of tertian infection is sure to be successful, at a given period of the disease, with a view of the forms known as gametes, and of the flagellates specially, we may follow the course of a quartan for weeks without finding even one. The first to speak of flagellate quartan bodies were Bastianelli and Bignami, the biological significance of which, reasoning by analogy, is that it is the same as that of similar bodies of æstival and tertian parasites ; and Thayer and Hewetson, who found them in two out of five cases, describe them as smaller than those of the tertian, and as differing in the nature of pigment which is found in the body from which arise the flagella, the pigment granules being larger and blacker. The movements of the flagella are apparently not slower than in the tertian. According to the same authors, on the whole, the quartan flagellated body resembles not those of tertian origin, but rather those of æstival.

CHAPTER VIII.

PARASITES OF TERTIAN FEVER.

In connection with the tertian parasites also there are two life-cycles to be considered, one of which is completed in man, while the other begins in man, but is completed in some species of mosquito. In most malarious regions this variety of the malarial parasites is very common. Where only mild types of malaria occur it is, as a rule, the prevailing, and sometimes the sole, variety observed. The tertian and the quartan parasites cause most, if not in some places all, of the winter and summer intermittents; but they, and especially the tertian parasite, may cause in districts of even severe malaria not a few of the malarial fevers of summer and autumn, although the more severe and irregular of these fevers are chiefly caused by the æstivo-autumnal organism. Still, severe as well as mild types of malarial fever may be produced by the tertian parasites. The phases of development of this parasite were differentiated from the quartan, and described in their essential characteristics by Golgi in 1886 and 1889. His first description has been added to, and in some points corrected, by Antolessi (1889-90); Bastianelli; Bignami (1890); and other observers.

The analogy with the crescent forms was proved by the two last-mentioned investigators. The life-cycle, which is completed in man, is in intimate relation to the successive febrile attacks; and the duration of this cycle, from the youngest forms to sporulation, is about two days. The time which elapses between the beginning of one attack and that of the next one is its equivalent. The tertian parasites become larger than a normal red blood corpuscle during the course of its development, that is to say, much larger than an adult æstivo-autumnal parasite, from which it differs not only

in size but in appearance, in the nature of the pigment, of the
sporulation, etc. . . .   The two species possess essentially
the same structure ; but the differences in pathogenic action
between the two is well known.   Under the microscope it is
very difficult to distinguish the young non-pigmented forms
from those of the æstivo-autumnal, as they are so similar.
They are usually a little larger and less opaque.   They are
very motile, and go through the usual change in form, pass-
ing from the descoid to the annular form, and from this to
the amœboid.   The forms in motion send out slender pro-
longations—*pseudopodia*—which may ramify in every direc-
tion, sometimes reaching the periphery of the red blood cor-
puscle, but not going beyond it.   The most varied and strange
forms imaginable result from the fact that they also then retract
and other similar pseudopodia project from other parts of the
parasitic body.   In the tertian parasites pigmentation occurs
with rapidity, while the similar non-pigmented phase in the
æstivo-autumnal is of long duration.   The pigment in the
initial forms is scanty, and in very fine granules, and has a
tendency to accumulate at the extremity of the pseudopodia.
The structure of the young forms is like that to be described
in the æstivo-autumnal parasites ; in properly-stained pre-
parations they are seen to be formed of cytoplasm which is
stained in Romanowsky's methyl-blue, against which is seen
the chromatin body stained purplish red, round or ovoid in
shape, and larger than similar body in the first stage of devel-
opment of the æstival parasite.   We see around it a slender
pale zone, which separates the chromatin from the cytoplasm ;
though we do not see it always in the æstival parasites,
except at a stage more advanced, it is constant in these
forms.   We see only the parts just mentioned in many endo-
globular parasites, and in those which are free in the plasma.
But in other endoglobular parasites we may find the charac-
teristic ring, that is to say, a blue ring which is, as a rule,
thicker in one-half than in the other, enclosing a space which

is of about the colour of the red cell, or a trifle lighter.   At
one point of the periphery of the ring we find the nuclear
formation mentioned, that is to say, the chromatin body surrounded by a pale zone.   In these forms it is readily seen
that we have not to do with a larger vesicular nucleus occupying the whole centre of the ring, but with a vacuole from
which the limiting outline of the clear zone serves to distinguish the nucleus embedded in the cytoplasm.   The most
varied forms are to be seen if the parasite be fixed during
amœboid movements.   The round or roundish vacuole is
usually found near the nucleus ; and from the surrounding
ring of protoplasm we see simple or ramified prolongations
projecting, which are sometimes very long.   Other non-
vacuolated forms may have the shape of a horse-shoe, or of a
slender filament of cytoplasm (the nuclear body being situated near one of the ends of this, or even at its end) curved
upon itself in various ways.   The special characteristics of
the tertian parasite are more in evidence in the forms of more
advanced development.   They increase in size, which is due
chiefly to the growth of the cytoplasm, there being no proportionate increase of the nucleus, is very marked, so much
so, that in the first twenty-four hours the parasite may
take up from one-half to two-thirds of the red corpuscle.

The parasite appears to have acquired more definite outlines in a fresh preparation ; it contains many granules of
melanin, and possesses lively amœboid movements, which
cause it to assume curious shapes within the corpuscle.
Even when the movements of the cytoplasm are not shown
by marked changes in the outline, we often see the pigment
granules change place, sometimes slowly, but usually with
great rapidity, looking very much like the darting of the flies.
This motion is believed to be due to the plasmatic current
like which it is more or less rapid ; it is not trembling in
character, neither has it the regularity of a Brownian movement.   That the parasite containing red blood corpuscles

are markedly larger and paler than normal is one of the most striking facts; indeed, the rapidity with which swelling and decolouration of the infected red cell occurs, is one of the most characteristic properties of the tertian parasite. During the second twenty-four hours the development of the parasitic body continues until it is about two-thirds to four-fifths the diameter of the enclosing corpuscle, which is usually the limit of the growth of the adult body. With the exception that the amœboid movements are a little less rapid for which reason it is apt to maintain a more or less rounded form, and does not assume the bizarre shapes seen in the younger stages,—in this last period of development it maintains the characteristics already described. What has been already said applies to its structure also. Nevertheless, the chromatin is a trifle less deeply stained than in the very young forms; and according to Romanowsky, it appears to be composed of very fine filaments and points, the latter probably represents the cross section of the filaments. The cytoplasm stained blue is found to have increased proportionately more than the nucleus and is markedly pigmented. The pigment does not naturally invade the clear zone which surrounds the nuclear chromatin, and which belongs to the nucleus-nuclear juice. The protoplasm is stained blue, but the colouration is not always uniform—the difference in thickness of its various parts caused by the amœboid movements probably accounting for this. In the forms which are as large as half the red corpuscle, we see a vacuole often in the cytoplasm which may be near the nucleus or at the periphery; there may even be two or three vacuoles. The form of the vacuole is not always circular, but often irregular, and not infrequently prolongations from the cytoplasm may be seen within it; these are evidently pseudopodia that were surpassed and fixed during motion. The chromatinic part of the nucleus is seen more clearly than in the preceding phase to possess a fibrillary appearance in the round but slightly motile adult forms.

On arrival at the stage of development, these changes begin
which lead to sporulation. The latter, as in the case of
æstivo-autumnal parasite, coincides with the onset of the
febrile attack and is completed within the corpuscle after about
48 hours. Scarcely anything of the interior changes which
produce fission is seen in fresh preparations ; we see the
pigmented body in the process of dividing, or already divided,
into daughter bodies, that is to say, only the result is
observed. Golgi, in view of the very varied forms seen in fresh
preparations, recognises several methods of segmentation in
the tertian parasite. The most frequent occurrence is to see
adult pigmented bodies, in which the pigment is more or less
entirely collected in the centre ; around this pigment mass
the parasitic body divides into a varying number of little
spheres, about 15 to 20, which altogether form a round
mass. They do not essentially differ from those forms in
which the pigment, instead of remaining at the centre in one
mass, is found at the periphery, or is divided into two or
three small clumps, or is irregularly disseminated between
the individual bodies.

The same author affirms that the segmentation in other
parasitic bodies may occur in a very different way, namely,
by the formation of figures resembling sunflowers. Accord-
ing to him when the pigment is gathered at the centre of the
parasitic body the peripheral portion of the latter appears to
separate itself from the pigmented centre in the form of a
ring. In this ring radiating striæ appear very soon which at
first are scarcely visible, but gradually become more and more
marked, and which subdivide the ring into numerous portions
composed of a whitish substance ; these subdivisions gradu-
ally become individualised, so to speak, acquire definite outlines
and form many little *spheres* which become detached from
each other, and finally arrange themselves in the form of a
wreath around a central pigmented disc. The author regards
this as the form of segmentation as most characteristic of the

tertian parasite, and the one differing most from the fission process of the other form of parasite. He also indicates a third method of segmentation seen in free bodies, but does so somewhat doubtfully. In these bodies he says, we occasionally observe that the "pigment, instead of being in masses at the *centre* as usual, gradually becomes arranged in a zone more or less close to the periphery, this occurring in such a way as to determine a somewhat distinct line of separation between the part occupied by pigment and that which is free from it. The latter becomes exceedingly transparent, sometimes appearing like a vacuole, within which may be seen one, or more, rarely several, *spheres* similar to those which result from segmentation." Nevertheless, later studies on the structure have shown that this is not a process of multiplication by segmentation but of degeneration, which occurs in the large pigmented bodies free in the plasma. The various changes described above *which* may be witnessed in fresh preparation in the fission forms occur with great rapidity at the onset of the attack, and represents only the latest phases of fission. During the microscopical examination all that we are able to see is the more or less rapid separation of the daughter bodies from each other ; but in blood taken from the circula-tion, that is to say, in the ordinary preparations, the various phenomena leading to formation of the individual parasites cannot be followed.

The fact that the gradual passage of the uninucleated adult body to a comparatively segmented form occurs in successive stages with marked slowness, the process sometimes taking more than twelve hours is demonstrated by an examination of *stained* specimens, specially those made after Romanowsky's method. This is fundamentally the same process as that, described later in connection with the æstival parasites; but, because of the greater size of the tertian parasites, it can be more clearly observed. The nuclear chromatin as we have already seen, in the adult forms

presents a less uniform and compact appearance than in the
young forms. When the stage of division approaches, the
filament of rods, which gives a lenticulated appearance to the
chromatin mass, tends to separate, leaving clear spaces
between them, so that the nucleus becomes two or three
times larger than the younger forms. At the same time, the
pale zone surrounding the chromatin becomes thinner and
less easily distinguished than before from the surrounding
protoplasm. The chromatin now divides into two masses
which sometimes take on the shape of semicircles, whose
concave surfaces face each other, and are then transformed into
more or less compact masses surrounded by a narrow, clear
zone. We have thus two new nuclei somewhat smaller than
the original nucleus. From this by a similar process of
division, with each act of which the clear zone surrounding
the chromatin becomes less visible, but again becomes more
distinct again after the formation of the new nucleus, are
formed other nuclei which having a tendency to separate from
each other, arrange themselves towards the periphery of the
cytoplasm. This clear zone is never invaded by the pigment.
The latter gathers in one or more clumps at the periphery or
at the centre of the parasite, being pushed away by the
successive division of the nucleus. Pigment bodies with two,
four, six or more nuclei are formed by these successive
divisions, which also lead to the formation of from sixteen to
twenty nuclei, which is the average number of spores
to which a tertian body gives rise. In preparations made
about six hours previous to the febrile attack, which
coincides with complete segmentation, one may observe
pigmented bodies with about eight nuclei, more rarely ten or
twelve. When the process of formation of daughter nuclei
is finished, a portion of the cytoplasm condenses around each,
becoming separated from the surrounding parts ; thus are
formed the daughter bodies, *spore* or *gymnospore*, which is
therefore composed of a small mass of strongly stainable

chromatin, surrounded by a narrow, clear zone, and by a ring of protoplasm which is of a deep blue colour. A portion of the cytoplasm which is less deeply stained, and which contains granules or needles of black pigments, remains unused and is called the *residuum* of segmentation. As a rule, the nucleus is eccentrically situated with reference to the cytoplasm. The red corpuscles, which in fresh specimens has become almost invisible from the gradual consumption of the hæmoglobin, at this time bursts open, possibly by reason of the swelling of the part of the protoplasm which represents the residua of segmentation, and the gymnospores become free. The diversity of the contradictory result obtained by observers other than Romanowsky, Ziemann, etc., whose idea of the process of fission, has just been given, is due to varying technical methods which they employed. Mannaberg, by staining with hæmatoxylin, was not able to observe the successive divisions of the chromatin, for which reason he believed that the chromatin, nucleolus, in forms about to divide, came out from the nucleus and mixed with the cytoplasm; therefore the stage in which the parasite is preparing to sporulate he considers to be characterised by the disappearance of the nucleolus (nuclear chromatin, *nucleoliform node*). But this disappearance in the case of the æstival parasite does not exist. The error probably arose from the fact that there is a phase in the life of the parasite in which the nuclear chromatin cannot be distinguished by the depth of the staining, hæmatoxylin method, from the cytoplasm, and this is precisely the stage in which the chromatin undergoes successive divisions. Now, regarding the forms which begin in man, the cycle which is completed in the mosquito, it may here be noted, that for a long time observers had perceived in the tertian blood in addition to the pigmented bodies which, when they reached the adult stage, underwent the modification described up to sporulation, there were others which, although they grew even larger at first, did not become

segmented, but underwent other transformations. In other words, they in part fell a prey to various degenerative processes, and in part flagellated. Celli and Antolessi looked upon these bodies which they first described as forms of degeneration. Their analogy to the crescent bodies was demonstrated later by Bignami and Bastianelli, who also held that here, as in the æstivo-autumnal species of the parasite, their significance is the same. In fresh preparations, in their adult forms they are seen as round or somewhat elongated bodies, sometimes with a long diameter twice the size of that of an ordinary red blood corpuscle ; the red cell containing them, is of course enlarged and pale, sometimes entirely decolourised. The protoplasm contains a large amount of black or brick-red pigment in most active motion ; and sometimes there may be found a somewhat large hyaline vesicle, usually eccentrically situated, and evidently representing the nucleus. This is perhaps the only form of the tertian parasite in which the nucleus is visible in a fresh preparation without any staining ; and it is likely that there is a nuclear membrane which is not visible in the stained parasites, as this nucleus has a distinctly vesicular appearance, and a decided outline which the pigment in spite of its motility, never goes beyond. Continuing to observe one of these bodies, we often observe that at one particular point a small transparent sphere is formed and around it a vacuole, then close to the first one other spherules and vacuoles appear, until the whole parasite has been converted into a mass of globules of varying size, between which are disposed the pigment granules, whose oscillatory movements cease entirely. Sometimes while this vacuolisation and progressive splitting of the parasitic body into hyaline spheres is taking place, a part of the cytoplasm projects beyond the red corpuscles ; and until this portion is also broken up into hyaline masses, the oscillations of the pigment continues. Both Celli and Antolessi were well aware that this process of

disaggregation and vacuolisation indicates the death of the adult parasitic body. The description given by some writers of reproduction with vacuolisation of the tertian parasites, a reproduction whose various phases can be followed by microscopic examination, corresponds perfectly to the phases of this degenerative change. The fact that sporulation always occurs in the characteristic manner is described above that it is not a multiplication.

During the time that some of these bodies are seen to become vacuolated and to divide into small transparent masses of unequal size, or to present both phenomena at once, others during the microscopical examination suddenly exhibit a confused movement of the cytoplasm and of the pigment contained in it, and then in precisely the same way as the round bodies belonging to the crescent stage becomes changed into flagellated bodies. From the pigmented mass hyaline buds are seen coming wh'ch give rise to flagella. When the movement of the flagella ceases and they have become detached and removed from the pigmented body, a sort of clot of pigmented protoplasm remains behind, and then divides into a variable number of transparent *spherules.* Soon after this all movement in the pigment ceases. The pigmented bodies—those which become flagellated as well as those which do not—in preparations stained by Romanowsky's method are seen to be composed of an abundant amount of cytoplasm, which is stained blue ; a vesicular nucleus, which contains threads or granules or rods of chromatin surrounded by a clear zone, is also present. Now, when these bodies remain in man they end in the generative process, and are taken up by the phagocytes, as occurs in the bodies of the crescent group. In fact in the examination of stained speci-mens we find a few which contain very little chromatin, or none at all sterile bodies as they have been termed. But when, in their adult stage, they are taken in with the patient's blood by the mosquito, they develop in the intestine of the latter

provided it belongs to the right species. Like the crescent form, they are held to be gametes; for their biological significance is identical. Their development has not been followed as completely as that of the crescent; still in preparations made after Romanowsky's method, Bastianelli and Bignami have observed parasitic forms about half the size of the adult bodies described, which are distinguished from the forms of the first cycle multiplying in man by the nature of the nuclear chromatin. Their chromatin is arranged in thread and rods, sometimes forming a sort of reticulum, and neither so compact nor so deeply stained as in the forms capable of sporulation. These bodies are probably forms of gametes in process of development. We cannot tell if the youngest forms are present in the bone-marrow, as in the case of the young crescents, by direct examination. It is believed by many that these large pigmented bodies represent the gametes of the tertian parasites; and the reasons for this belief are the same which have been given in the case of the crescent forms, that is to say, reasons based upon morphological studies and upon analogy   It follows that these parasitic forms, like the crescents, should be divided into two classes, namely, the *macrogametes*, those which do not become flagellated, and the *microgametocytes* or those that do. Preparations of tertian blood, kept in a moist chamber for twenty minutes, dried and stained by Romanowsky's method, will suffice for the demonstration of the differences between the first and second. We find the nucleus in the first to be somewhat swollen and situated at the periphery of the protoplasm. In the second, or microgametocytes, the nucleus is at the centre of the parasite; and it contains a large amount of chromatin, five or six times as much as in the macrogametes, which is gathered in apparently a single mass at the centre of the nucleus, or as deeply stained intertwined threads. From these bodies arise the flagella microgametes by a process which, to judge from the transitional forms,

may be described as follows:—The chromatin (all of this being used up in the formation of the microgametes) divides into a number of small masses which are carried to the periphery, each mass then becoming transformed into a filament which projects from the parasitic body, and is surrounded by a thin layer of protoplasm. The above description of the flagellata of crescent origin does not exactly apply to these *tertian* pseudo-flagellata; for here the number of flagella is usually greater; as a rule, they contain six, and in their entirety they are larger. The formation of the *microgametes* in their normal surroundings, the middle intestines of *anopheles*, occurs in the same way. The fecundation of a *macrogametes* by the entrance of a flagellum appears to take place in this locality. The tertian parasites will already be found in a condition to develop in the mosquito if a patient suffering from primary tertian infection be stung a few days after the beginning of the disease. The further development of these bodies, which are already found at an adult stage in the blood of patients with tertian fever a few days after the onset of the infection, has been already described.

CHAPTER IX.

PARASITES OF ÆSTIVO-AUTUMNAL FEVER.

The small protoplasmic bodies (which are found either adherent to the surface of the red blood corpuscles or in a sort of niche on their surface or edge, or else within their substance, non-pigmented plasmodia or amœba of Marchiafava and Celli) represent the young forms of these parasites. They may be endowed with lively amœboid movements, or immotile, discoid and annular forms. The endoglobular forms are those undergoing development, and we find in them very fine granules of black or brown pigment arranged, with more or less regularity, at the periphery of the parasitic body (forms with pigment granules); these may move like small amœbæ or be immotile (discoid or annular). The pigment at the periphery of the parasites, in the more advanced stages of endoglobular life in which the parasites are preparing to multiply, shows a tendency to gather at one point at the centre or slightly eccentrically (forms with blocks of pigment) or in one block or in a thick mass of black granules. While the young non-pigmented forms, as well as those in process of development, are found circulating in the peripheral blood, the bodies with blocks of pigment are found accumulated in the vascular system of the viscera, spleen, bone-marrow, brain in cases of pernicious fever, etc., excepting in very grave infections, in which they may be found in the circulating blood. One of the most characteristic of the æstivo-autumnal parasites, as distinguished from the other species, is constituted by this distribution of the various parasitic forms in the vascular system. The parasite body, in the forms with blocks of pigment, divides into a variable number of round or ovoid bodies, all alike and of the same size, which arrange themselves usually in a single or double

wreath around the pigment. This segmentation which occurs within the red corpuscles, whose size the parasite does not attain even at its most advanced stage of growth, constitutes the mode of multiplication of the parasite in man (fission or sporulation form). In the vessels of the viscera these forms are found stationary, like those of the preceding stage. New red corpuscles are invaded by the little bodies resulting from fission, and they commence the life-cycle just mentioned. Because of its intimate relation to the development and succession of the febrile attacks these successive phases of existence constitute the human cycle of the parasite, or, as it has also been called, the *pyrotogenous cycle*. It is not in this way that all the parasitic forms develop. In all cases, a certain number of young pigmented bodies continue to grow and become ovoid or spindle-shaped, while the pigment increases in amount and takes on the appearance of needles or little rods. One will usually observe a curving into a crescentic form, (body No. 1 of Laveran, crescents, ovoid, and fusiform bodies), when these fusiform or ovoid bodies by their increase in length have become longer than the diameter of the red corpuscles in which they have developed. In ordinary fresh preparations, if observation be continued for some time, these bodies, which begin in man the life-cycle which is continued outside of the human body, are seen to present certain important life phenomena. After ten minutes, or even more, we see that while certain of the crescents persist in their typical form, others become ovoid and then round. Then in the round bodies, the biological significance of which can only be understood by following the later phases of development in the mid-intestine of the mosquito, there begins an active movement on the part of the granules or rods of pigment, followed by the tumultuous thrusting forth of several filaments, usually four, which move like flagella. They usually become detached and continue to move with the greatest rapidity among the red corpuscles

(body No. 2 of Laveran, flagellated body of the majority of
writers). In the crescent phase these forms represent the
beginning in man of a cycle of life which is continued and
completed in the mosquito. Unlike the forms of the first
cycle, they have a pathogenic action in man ; and because
their development has been seen only in some species of
mosquito belonging to the genus *Anopheles*, they have been
termed forms of the *Anophelic cycle*. To commence with the
bodies of the pyrotogenous cycle, *i.e.*, the young non-
pigmented parasites or the non-pigmented plasmodia of Mar-
chiafava and Celli, we may note that these forms seen
in fresh preparations, occur as small whitish protoplasmic
masses, possessing rapid amœboid movements, which take
place at the ordinary temperature of the atmosphere from
July to October, and are quicker than those of the leucocytes
at the same temperature. In a state of rest they are discoid
in shape ; from this form they pass to the most varied shapes,
such as stars, crosses, and other odd forms, pushing out
slender, diaphanous prolongations which oscillate in the
substance of the red cell ; they sometimes even ramify and
then become retracted, while new ones are pushed out at
other points of the periphery. After a while they become
round again. At the ordinary summer temperature these
movements may continue from twenty to forty minutes,
sometimes as long as five hours. When they have ceased,
or are about to cease, they can be revived by using the warm
table, and by passing through it a current of water at 102° to
104° F. Sometimes the little body moves as if it were about
to emerge from the corpuscle, but its pseudopodia never go
beyond the limits of the red cell. When it stops moving it takes
on a circular form, which is whiter at the periphery than in the
centre (discoid form). Careful observation of one of these
discoid forms shows that the central part gradually becomes
differentiated more and more from the periphery ; little by
little it loses its whitish aspect, and through it can be seen

the hæmoglobin of the red corpuscles; the periphery, on the other hand, becomes more distinct and of a shining white tint, as if it were thicker.   Thus is formed a distinct ring, which looks as if it were printed in the red cell (*annular* form) ; and this is a more prominent form than the peceding one, by reason of its greater refractive power.   The aspect of these small rings may be seen to undergo alteration; the cytoplasm, which forms the ring, spreads towards the centre which resumes its whitish diaphanous appearance, and it also spreads peripherally, the parasite thus becoming larger and of a more uniform appearance.   It gradually returns to its discoid shape, which is larger than the ring from which it starts, and into which it may again become changed. Amœboid movements, but slower than before, may again be observed in connection with the ring which has become discoid.   By examining one parasite only with a homogeneous one-twelfth immersion lens, this succession of form—*amœboid, discoid*, and *annular*—may be easily followed.   It was by this means that these little bodies were seen and described by Marchiafava and Celli who, having at first limited their investigations to primary cases of grave æstival infection, which seemed to lend themselves most readily to the study of the malarial parasite, were led to attribute the greatest importance to these little bodies.   In these cases, in fact, the above mentioned bodies are those which chiefly attract the attention of the investigator ; and the strongest impression of a living being is given by this, amongst all the forms assumed by the malarial parasite, by its especial characteristics of motility.   When in a state of rest (discoid form) these young forms closely resemble *discs*, that is to say, they are so flattened that their lesser diameter corresponds to the thickness of the red blood cells.   This is seen obliquely in the rare cases in which the little amœba turns upon itself, but very often when it is endwise presented to view.   An estimation of the true significance of the annular bodies is a matter of much

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more difficulty. Marchiafava and Celli held that the so-called rings, which are so plainly seen as if printed on the red corpuscles, were merely amœboid bodies which, becoming very thin at the centre, allowed the central part of the corpuscle to be visible through them ; by this thinning of the central portion and consequent thickening of the peripheral zone, there is formed biconcave lens-shaped figures, somewhat resembling corpuscles itself. In fact, if we observe one of these ring-shaped bodies when it presents itself endwise, which, as we have seen is rare, but still may occur, we have actually the impression of a biconcave lens. Antolessi, who thought from the absence of analogous facts, it was highly improbable a living organism could take on such an appearance, held that the annular forms were merely small amœba which had included in their substance a small particle of the red cell, as Osler and Councilman first suggested. Taking into consideration the way in which a discoid form is seen to become annular during the microscopical examination, one can hardly accept Antolessi's view. Were it correct, we should see the amœboid parasite when about to become annular, lengthens itself like a rod, then curve like horse-shoe, and finally unite the two pseudopodia after having included a portion of the red cell ; in fact, the thing would have to occur as it does when an amœba or a leucocyte invades a foreign body. The fact that it occurs in an entirely different way has already been demonstrated There are many who assert, and there seems no reason to doubt the hypothesis in question, that the annular form represents a parasite with a central vacuole, around which the substance of the amœboid body arranges itself in ring form. It is easy to understand why, on the examination of a fresh ring specimen, the ring seems to be entirely absent at the centre, and seen endwise, it has the appearance of that of a biconvave lens ; and this so because the vacuole is transparent. It must, of course, be distinctly understood that there can be no doubt that there are forms of the annular body which are

nothing else than young parasites which have included a
portion of the red blod corpuscles, as Osler, Councilman, and
Antolessi affirm. But these must be distinguished from typical
annular forms, which, as can be seen from the description,
are merely parasites whose protoplasm has contracted in ring-
shape around a diaphanous, very transparent substance,
which substitutes the vacuole. This vacuole disappears
in the bodies of the next phase when the stage of nuclear
multiplication approaches. It is also worth remembering
that it disappears likewise in the cadaver; indeed, in the
cadaver we do not see annular bodies, but only, as a
rule, immotile discoid or spherical *micrococciform* bodies.
Annular bodies also disappear from the malarial blood which
has been strongly cinchonised. All this leads to the belief
that we have to do with a vacuole which, in the nutrition of
the parasite in its young stage, is of very considerable
importance and significance. Nevertheless, it is in an entirely
different manner that the forms which include a particle of
the red blood corpuscle behave. First of all, whether the
parasite be immotile or in motion, the included parasites
may always be seen and followed, while in the annular
forms the vacuole becomes invisible so soon as the para-
sites alter their shape and put out pseudopodia. More-
over, in the particle of included hæmoglobin, we often see
brown granules of melanin which have come from the
transformation of the hæmoglobin, while nothing like this is
ever seen in the central portion of the annular form; but even
before the transformation of hæmoglobin into melanin has
begun, we can see that the included hæmoglobin is of a
darker colour than normal and somewhat resembles brass
that is old. Finally we may see plasmodia with fragments
of included hæmoglobin in the cadaver, and in strongly
cinchonised blood; while in blood under such circumstances,
the annular forms are not to be found. The following
description applies to the structure of these young forms a

shown in preparation stained by methylene blue or by hæmo-
toxylin.   There is a very thin ring which is coloured blue or
violet, and which is deeper and thicker in one half than in the
other ; the ring surrounds a space which takes the same stain
as the red corpuscles, specially in its youngest stage, while
in the centre of more developed forms the red corpuscle is of
a paler appearance than is the outside of the ring ; there is,
therefore, in this form a very diaphanous portion of the para-
sitic body, which prevents a perfect appreciation of the colour
of the corpuscle.   In the thickness of the stained ring we see
one, and not infrequently two or more very small granules of
chromatin, which, treated by Romanowsky's method, are
clearly visible against the blue substance of the ring, being
stained red or purplish-red.   Around the chromatin granules
we do not see a clear hole, or the constituent parts of a true
nucleus, as we do in part at least in the surrounding
phases.   We have already seen that the chromatin forms
a part of the coloured ring ; in fact, in the majority of
parasites, it is intimately connected with it ; in some it seems
to project from the ring into the substance of the globule,
in others, but rarely, it is found in the centre, and is not
connected with the peripheral coloured ring, in any percepti-
ble way.   As was pointed out by Marchiafava and Celli, as
early as in 1883, in cases in which the blood is fixed while the
young parasites are in motion, we do not see them occurring
as regular circles, but with deformities and prolongations.
The appearances just described can be explained in view of
the fact that the little body of chromatin represents what is
rendered visible by our technical methods of a nuclear forma-
tion which is apparently very simple , the blue ring is the pro-
toplasm of the parasite, which includes a central transparent
portion, *i.e.*, a nutritive vacuole.   In preparations which are
properly stained, the aspect of these forms renders them
clearly distinguishable from the irregular spots stained
by the basic *aniline* colours which are seen within the red

corpuscles, coloured dots and spots, the nature of which has
been variously interpreted by different authorities. One not
infrequently sees, in the red corpuscles, and in addition to
ordinary vacuole, portions completely deprived of hæmoglo-
bin, which may be of various forms : some occur as hyaline
rods, some as very small round bodies, as rods curved in a
horse-shoe shape and even rods, elongated into spindles
with a point at the centre or nearer to one or the other
extremity, which is about the colour of the red cell, or little
darker ; these last are the forms which may be easily mistaken
for the rings. Finally we may see, but rarely, small shining
white rings. All these forms which resemble the young
non-pigmented plasmodia are not infrequently seen in the
blood of patients suffering from various diseases, but more
especially from tuberculosis, typhoid fever, pneumonia, and
suppurative fevers ; as a rule, they are few in number, but in
some cases they are fairly abundant. An experienced
observer has no difficulty in distinguishing these alterations
(the little bodies in question when stained or seen to be
devoid of characteristic structure) of the corpuscles from
young plasmodia ; it is only necessary to see the special
refraction of the hyaline bodies, which are much greater
than that of the parasites. If we watch the succession of
the forms above described, from the annular to the discoid
and to the amœboid, the diagnosis of parasites will be
assured. Indeed, confusion is impossible if we continue
the observation of the suspected bodies, which may, it is
true, like the vacuoles, exhibit slow alterations of contour
and even oscillate as if they were about to turn around on
their own axis ; but we never see any movements even
faintly resembling amœboid motility. Regarding the
plasmodia with pigmented granules, *i.e.,* the forms in process
of development, although no black pigment granules are
discernible even on the most careful observation, the young
parasites just described increase somewhat in size, and begin

to show a slight darkening around the contour. Preceding the pigmented phases, are to be seen forms which have included a portion of the red blood corpuscles, clearly distinguishable from the annular forms, which, while under observation, become slowly modified in colour and darkened. The pigmented phase is represented by parasites a quarter or a third the size of the red corpuscles, with very fine granules of pigment, which are usually collected at the margin, but are sometimes scattered within the protoplasm of the parasite. It must also be remembered that in many forms the pigment is only apparently marginal, because the peripheral granules at the border, between the parasitic body and the substance of the red corpuscles, are more clearly seen than the others. Many parasites at the same stage, as the preceding, are of much smaller size. The pigment granules are for the most part immotile, but they may also sometimes oscillate like the pigment of the parasite in ordinary tertian, specially in the larger forms. These pigmented bodies may take on the same form as those of the preceding phase, or present an *annular*, *discoid* and *motile* form. The *annular* forms are smaller than the discoid and motile ones as though they are contraction forms, and capable of returning easily to the motile condition. The *discoid* forms have often a crenated outline ; and the *motile* forms may take on strange shapes, such as the *dentritic*. One must be very careful, even in this phase, to distinguish the annular forms, properly so-called, which contain one or more fragments of hæmoglobin. The differences are the same as those before described. The first have the appearance of a shining ring, one-half of which is thicker than the other, sickle form, with the centre showing the red corpuscle of proper colour or paler than normal ; when they become motile again, they spread out, become diaphanous more than before, and in the central portion take on a colour like that of the periphery of the parasite, but usually fainter.

The parasites that hold a fragment of hæmglobin may assume any shape without the fragment becoming invisible; this fragment has a tendency, even when the rest of the globule is of normal appearance, to become brassy, and is darker than the red blood corpuscles. Until the initiation of the changes which lead to multiplication by fission, the amœboid movements of the parasites continue to be very active during this phase. By a diminution of motility and by an increase in size of pigment granules, and a tendency on their part to collect into group, the next stage is gradually reached. As the parasites develop, the pigment granules, which at first were almost imperceptibly small, become larger and tend to coalesce into three or four small masses, which then take up an eccentric position: at this stage the parasite is more rarely of the dentritic form just mentioned, but usually becomes discoid. By the usual process of staining, it is evident that the structure is the same as in the preceding stage. The parasites occur in rings, which are readily stained by hæmotoxylin, methylene blue, etc. The coloured ring, at the margin of which the pigment is chiefly found, is not of uniform thickness, but usually *falciform*, this *falciform* appearance being even more distinct because of the increased size. In situation and other particulars, the chromation globule, which is larger than in the preceding stage, is the same. In preparations stained according to Romanowsky's method, this globule, which is coloured violet red, appears with great distinctness upon the blue ring of protoplasm. In the more developed forms, we find that it is usually surrounded by a pale zone, which is, as a rule, not visible in the preceding stage; it is not homogeneous, but is composed of filaments and rods of chromatin. From this, then, it is evident that the parasite consists of a little mass of chromatin, the chromatin sometimes occurring in threads, surrounded by a halo of a pale substance, both together constituting a nucleus, and of a protoplasm containing black granules, which is

disposed in annular form around a vacuole. In the more advanced forms of development, and therefore nearer to the next stage of development, the vacuole is no longer to be found ; in this case the parasite consists of protoplasm, which is specially pigmented at the periphery, and of a somewhat larger nucleus with distinct outline, in which is seen clearly the chromatin and the pale substance surrounding it. The latter is probably nuclear juice. The division of the nucleus is the chief characteristic of the stage which consists of parasites in process of division, that is to say, of bodies with central or eccentric blocks of pigments. Divisions of the protoplasm, with the formation of daughter forms, or so-called spores, follows the division of the nucleus, which latter goes on till a variable number of very distinct nuclei have been formed. Now, if we begin with the body of the preceding stage, we can follow them as they increase in size ; the pigment also increases in the form of fine granules, which tend to collect into large granules, and finally in a block or clump of granule gathered at the centre of the parasitic body, or else situated eccentrically, or even at a point in the periphery of the body itself; these clumps may be two or three in number, or exceptionally even more, but in this case each one is naturally smaller than the single block which is the usual form   Rapid oscillating movements may be observed in the pigment when it is collected into little granules or rods, or the same may not be capable of any motility. Though the average size of these bodies is about a third of that of the corpuscles, it may vary from a quarter to a half of that of a red blood cell. But some are so small as not to fill the corpuscle, even when two or three or more of them are aggregated therein. It is in fresh preparations that the structures of these little bodies are best seen ; they appear to be composed of protoplasm which is rather highly refractive, and to be homogeneous. At the periphery a series of shining dots indicative of an advanced stage of the process of division will be seen in the more

progressed stages of development. These bodies are found to consist, when stained with hæmotoxylin in preparations dried according to Ehrlich's method, and fixed in absolute alcohol and ether, of which one part is coloured a deep purplish blue, usually at the periphery of the parasite, and of another very slightly stained and less extensive than the first, which corresponds with the pigments. In many of these bodies the mass of chromatin cannot be made visible by this method, which circumstance has suggested to some that it is dissolved and mixed with the protoplasm. Towards the periphery of the stained portion of the protoplasm, a variable number of minute bodies, of a more intense blue colour, which represent the chromatin bodies of the future spores, are to be seen in a more advanced stage of development, that is, in one nearer to multiplication. From this it follows that there is a stage of development during which the chromatin cannot be demonstrated; and also that another stage, in which the chromatin globules, together with blocks of pigments, again becomes distinctly visible towards the periphery of the parasite, follows this one. The chromatin is stained a different colour from the protoplasm in Romanowsky's method, and in it the process of nuclear division can be followed much better uninterruptedly. Then the chromatin in every stage of development is clearly to be distinguished from the protoplasm, it being of a purplish red, while the latter is of a more or less deep blue. By this method, indeed, we find that some of the bodies with blocks of pigment, usually the smallest, are composed of a peripheral portion stained blue, the protoplasm, and of a central or subcentral part formed of granules or filaments stained red, chromatin, surrounded by a pale substance, the nuclear juice, which remains almost or altogether unstained. By the side of these are seen other bodies with blocks, usually larger than the preceding, in which there are two or three clumps of chromatin, each one surrounded by a zone of a pale substance. These small

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masses, seen under a high power, appear to be *dentate* at the periphery, and to be composed of filaments so closely packed, that in some specimens they cannot be clearly distinguished. In other specimens each of these collections of chromatin filaments is seen to divide into two distinct masses, which are at first very closely packed together, but later on separate, and are then surrounded by a pallid zone, and arranged with more or less regularity in the protoplasm. Thus, by a successive series of division of the protoplasm, there occurs at this point the division of the body with the block of pigment into daughter bodies of the nucleus, we have the formation of a varying number of little round or ovoid bodies of chromatin which are readily stained and are compact in appearance, that is to say, without recognisable structure and apparently homogeneous. There is evidently a notable increase in the amount of the chromatin during the process of successive divisions of the chromatin. In each successive phase the amount is greater, and in comparison with that of the chromatin in the original solitary nucleus, that found in a body with a block of pigment in which the daughter bodies are already formed is very great. Coming now to the multiplication, fission, or sporulation forms, the first thing that we have to note is that when the nuclear chromatin has, as described in the preceding stage, been successively divided into a varying number of ovoid or rounded bodies, a portion of protoplasm arranges itself about each one, which then also divides ; and thus fission is complete, a very small portion of protoplasm with melanin remaining non-utilised, and forming the residuum of segmentation. These forms which have undergone fission appear in fresh specimens like an accumulation of round or ovoid bodies gathered around a block of melanin, and occupying from a third to a half of the red blood corpuscles in which they are situated ; there are forms both smaller and larger than this. As in the spores of the quartan parasite, in each of the daughter bodies we see for the

most part of a small shining spot. The number and struc-
ture of the spores can be estimated exactly in stained pre-
parations. Their number is somewhat variable ; some small
fission bodies with only six, eight, or ten spores take up not
more than a quarter of the red corpuscle ; other larger ones,
also endoglobular, have spores which form two rows around
the block of pigment, and are as many as thirty or even more
in number. In number the spores average from 14 to 16.
If we examine an individual spore, we see that it is com-
posed of a little chromatin body, which is very strongly
stained. It is called the nucleiform body, and is surrounded
by a thin stratum of protoplasm. The form is round or
ovoid As a rule, there is a zone which is not visible. It is
a pale zone, as in the spores of the tertian or the quartan,
around the nucleus ; and it is to be found in only a few of
the sporulating forms. The red corpuscle bursts open, and
the liberated spores disperse in the plasma, when fission has
occurred, perhaps as a result of swelling of the pale sub-
stance which is situated between the individual spores and
constitutes a part of the residuum of segmentation. This
exit of the spores can easily be seen under the microscope.
The freed spores adhere to new blood corpuscles ; and in
grave cases we may see two, three, or more spores clinging
to a corpuscle. These are easily distinguished from young
parasites by the fact that they have a determined and con-
stant form which is round and ovoid ; that they do not
possess amœboid movements, and that there is no vacuole
present. Upon the formation of a vacuole the young amœba
assumes, in stained preparations, the typical annular appear-
ance which differentiates it from the young bodies resulting
from fission. The transformation of the so-called spore into
a young amœba occurs with the appearance of amœboid move-
ments and of the vacuole, which, it is to be assumed, plays
an important part in the process of nutrition. It is probably
as degenerative products, and not as spores, that the bodies

resulting from the segmentation of an adult parasite must be regarded if they do not conform to the above description. In a fresh specimen we can not with certainty recognise an isolated spore, but must have recourse to appropriate staining. Spores in a fresh specimen can be recognised only when they are grouped in a characteristic manner. Not all parasites with pigment blocks give rise to multiplication form such as have been described above. Another process, which can be seen in every stage, and which is evidently of a degenerative nature, is that some swell up, or feebly stained with aniline dies, become vacuolated, and disintegrate into small, unequal, pale masses. It is now generally believed that about 48 hours are occupied, giving the tertian æstivo-autumnal fever, by the life-cycle just described, from the non-pigmented forms to sporulation, with the invasion of new red blood corpuscles. A study of the febrile curve shows that a rythm in the fundamental febrile type is clearly to be recognised, just as a study of the life-cycle demonstrates that the irregularities in its duration occur only within determined limits. It is believed that there is a variety of the same species, which completes its cycle in about 24 hours, giving a quotidian fever, but this point is still disputed by others. The duration of the human life-cycle of this parasite is neither so regular nor so constant as that of the quartan, but has certain oscillations and irregularities ; these are, however, not sufficient to justify the opinion of some authorities who refuse to recognise any law in the duration of the development of the parasite, or any type in fevers, the fevers producing it. The semilunar stage (of crescents, ovoid and fusiform bodies, round bodies of crescent origin, and flagellated bodies, regarding the origin of which, and the terminal phases, and the biological significance and the structure, there has been considerable disputation) represents the forms which begin in man the life-cycle which is completed in the mosquito. The mere mention of the name is sufficient to indicate the shape of the

crescents. They are cylindrical cells thinner at the two extremities than in the centre, transparent and colourless, a little longer than the diameter of the red cell, from 8 to 10 micromillimetres, and in breadth one-third the same diameter, 2 to 3 micromillimetres, curved in the form of a crescent ; in the central portion are grains of needle-shaped rods of melanin. The two ends of the crescents appear to be united in the concave side by a very fine line. The outline of the parasitic body is indicated by a single very fine line ; in some cases this may be double. The name also indicates the shape of the fusiform bodies, which form is most frequently seen in grave infections and pernicious fevers. The size of the fusiform bodies is about that of the preceding forms, which they resemble in all their characteristics, except that they are not curved upon themselves. As a rule, their ends are very slender ; the pigment may be gathered at the centre, and may be irregularly scattered in the parasitic body, or be arranged along the long axis of the spindle. The pigment is irregularly scattered, or more often collected in the central portion and arranged in the form of a wreath, in the case of the ovoid bodies. The latter also are shorter and thicker than the crescents. There is no amœboid movement to be observed in connection with all these forms, and the pigment even is immotile. As a rule, however, when they are carefully examined under the microscope, we see some changes in their shape, thus we may see a crescent become ovoid, and then become transformed into a round body, with a wreath of pigment also. It is long since to become apparent to the observer, that all are endoglobular ; and the very fine line which appears to unite the two curved ends of the crescents was regarded as the faint outline of the red blood corpuscles. The corpuscle which contains them is always very pale ; and sometimes, while the blood cell is pale, the crescent form has a slight *hæmoglobin* tint, as though it had attracted to it the colouring matter of the corpuscle,

forming of it a sort of cuticle. Their endoglobular nature
is now undisputed, though Laveran held that all the crescents
were simply adherent to the globules, and that this adhesion
was merely accidental. A crescent body appears to be
formed of a vesicular nucleus in the centre of the parasite,
around which are arranged needles or rods of pigments.
There is no membrane ; and we have also to note cytoplasm,
which surrounds the nucleus, and is more abundant in the
portions corresponding to the greatest diameter of the fusi-
form body. Authorities have been at variance as to the
presence of a membrane. Laveran, regarding the crescents
as cystic bodies, though there was a membrane ; but this was
disputed later, as a result of their microscopical observations,
by Marchiafava and Celli, in the year 1887. Still later in
1889, Celli and Guarnieri interpreted the double outline,
which is seen in some but not in all the crescents as
indicating the existence of a rather thick membrane. The
same theory was held by Mannaberg, who regarded the
crescents as *syzygies* resulting from the fusion of young
parasites, and therefore provided with a membrane. It is
true that the double outline is not seen at all, but only in a
few crescents, but it remains when these change into spheri-
cal bodies. It is true also that this double outline is seen
only in fresh specimens, and not in stained preparations ;
but Mannaberg rests his belief in the presence of a membrane
chiefly upon the phenomena that occur during the process of
flagellation. Nevertheless, the same phenomena may also be
seen in the flagellation of the tertian bodies, that is to say,
rapid undulatory movements of the contour of the parasitic
body, and active movements of the pigment-phenomena
which give the impression of the existence of bodies
moving rapidly within a cyst ; and yet, according to the
concensus of opinion, these have no membrane. A precon-
ception resulting from the long persistence of these bodies in
the patient's blood, in spite of the administration of quinine,

which appears to have no action upon them, is the theory that the crescents have a membrane ; and it is the result, not of the direct observation, but in consequence of the preconceived notion that the crescents are resistant bodies. Antolessi would seem to have given the correct interpretation of the double outline seen in some of these bodies. He considers it to be a series of hæmoglobin cuticle formed from the red corpuscle, within which the crescent has developed. As to the round adult bodies of crescent origin, they have a sort of adventitious envelope, formed from the peripheral portion of the red cell which has gradually become more or less invaded by the parasite. The existence of these pseudocysts explains the impression, the impression of a sudden libera-tion of the flagella from a restricted space in which they have been confined, conceived by an observer the change of a body of crescent origin into a flagellated body. In stuyding the structures of these bodies according to their method of methylene blue dissolved in *acetic fluid*, Celli and Guarnieri noticed that at the centre of the crescent, and close to the clump of pigment, was a small round body which was often stained blue, and which, according to these authorities, was similar to the little bodies which in the coccidia are regarded as nuclei. Later Grassi and Fletti described in the cres-cent a vesicular nucleus which for the most part was round, situated in the middle of the crescent body, and provided (sometimes, however, it was not discernible even when the method described was employed) with a chromatin body, which these authorities called the nucleoliform node, which might be large or small, and which is divided into two or four. By Mannaberg's method we frequently do not succeed in demonstrating the presence of chromatin in all crescentic bodies ; by the hæmotoxylin method of Bastianelli and Bigna-mi, in the majority of instances, the so-called nucleus cannot be seen, a fact which caused these observers to suppose that this formation was absent in bodies in the semi-lunar phase ;

specially as by the use of the same method they were always successful in finding the chromatin in the other phases of the æstivo-autumnal parasite. Since then, however, Ziemann believes that he has provided a morphological basis for the opinion that the crescents are sterile bodies ; and this he claims to have effected by adopting Romanowsky's method, affirming, that as a rule the crescents do not possess nuclear chromatin. Still, it is a fact that it was in consequence of the adoption of the very same method that Bignami and Bastianelli came ultimately to modify their early views upon the subject. They found that if preparations of blood were made in the usual way and kept in a moist chamber to prevent rapid drying, and then stained by the method in question, nuclear chromatin was clearly seen in all the crescents, as well as in the ovoid and round bodies of crescent origin. The protoplasm was of a more or less intense blue colour, and the nuclear chromatin occurred in the form of violet-red granules. The granules of chromatin were hidden by those of melanin surrounding it in Ziemann's case ; and this is probably why he, working with preparations which dried immediately after mounting, did not observe the same. In preparations kept in the moist chamber, however, as the nucleus and the body of the crescent swell and the pigment needles disperse, the chromatin becomes invisible, somewhat swells, and is stained by Romanowsky's method in the typical way. It is apparent because the chromatin in the crescent bodies is much less readily stained in the case of the young parasite forms, that there is difficulty in demonstrating it by means of the other method, which, as we have already noted, give results that are not constant. For a considerable time past, the researches which have been carried out as to the origin and development of the crescents have shown that the bodies of the semi-lunar stage are developed from the æstivo-autumnal parasites, of which they represent a life-phase that is constant. Even

when they are less than a quarter of the size of the red blood corpuscles, the young parasitic forms, from which the crescents originate, are distinguishable from the other forms of this species of parasites. They occur as small, round, ovoid, or spindle-shaped bodies, which, when seen in a fresh preparation, appears to be quite homogeneous, and to contain a greater amount of black pigment than do the bodies of equal size of the preceding cycle. The pigment, moreover, is in the form of little rods of somewhat large granules ; and it is either irregularly disseminated in the body of the parasite, or collected chiefly towards the periphery. In their development these forms always tend to adapt their convex surface to the edge of the corpuscle itself ; they are not motile ; and they always occupy the lateral portion of the red blood cells. Even the bodies which were originally round, with the progress of their development, tend to take on a long ovoid, or rather spindle-form, so long as the distance between the poles of the ovoid or the spindle does not accede the diameter of the red blood corpuscle. It either keeps the same shape, or becomes curved and forms the true crescents, when the said distance is exceeded. There is a correspondence in the structure of the young forms with that of the adult bodies. One may observe, when stained with Romanowsky's method, a cytoplasm, which is coloured blue more deeply at the periphery than towards the centre, and a nucleus, which in the young forms is rather large in proportion to the amount of cytoplasm ; the latter during the further development increases in volume much more than does the nucleus. The nuclear chromatin is stained a purplish red, and is usually in the forms of threads or rods, sometimes of granules. In some cases, it collects at the centre of the parasite, and is surrounded by a pale zone ; in other cases, again, the granules or threads of chromatin are disseminated more or less irregularly in the parasitic body, but this latter appearance may possibly be due to some accidental variation in the preparation of the specimen.

The young bodies, therefore, of the crescentic stage are distinguished from the parasites of equal size belonging to the first, or *pyrologeneous*, cycle as regards the character and deposition of the chromatin. In the case of the peripheral blood, the various forms of development of the crescent body are rarely to be observed ; for in it we usually find only the adult forms, the young forms occurring there only in grave infections with a large number of parasites in circulation, and not always then. The accumulation of young crescents in the bone-marrow was noted, several years ago, by Bignami and Bastianelli ; and the absolute exclusion of the possibility of this accumulation being an accidental circumstance has not been warranted by the results of autopsies in cases of grave infections. In the spleen we may find crescent bodies, and follow their endoglobular development, even when they are not found in the blood taken from the finger. It is in the case of pernicious fevers that a large number of young crescent bodies are to be found in the bone-marrow, and even when the same forms are very scarce in, or altogether absent from, the blood in other organs. These facts suggest that the bone-marrow is the chief, if not the exclusive, seat of the formation of the crescents. In spite of the above, Mannaberg believes that the origin of the crescent bodies may be explained on his theory that they are *syzygies* derived from the fusion of several young parasites ; as to the mode of multiplication, he maintains some reserve, but holds that it is not impossible that there is a segmentation along the minor axis. His hypothesis is based upon what he believes to be an established fact, that the crescent possesses a membrane and upon the theory that the young forms, of which several were found within one red cell, and by merging into one body ; the *syzygy*, according to his theory, is capable of multiplying later, and by its accumulation gives rise to the relapses. He, in view of the fact that often several young parasites are to be seen in the same

red blood corpuscle, and sometimes as many as six or seven appearing when very close together to be intimately adherent, draws all the forms which might be considered as transitional between the young crescents and the flattened parasites, and fully describes them.　His theory has not been allowed to pass unquestioned; for it has been urged against it that, in the first place, it cannot be held to have been conclusively demonstrated that the young parasites collected within one red corpuscle, become merged together : on the contrary, they follow their own development, as shown by the fact, that we often find several forms in process of multiplication within the corpuscle, or various amœboid forms in process of development.　In the second place, the crescent forms, as we have seen above, do not possess a membrane of their own, but a species of adventitious membrane formed from the red corpuscle ; and it is here to be noted that the formation of *syzygium* is usually followed by encystment.　In the third place, there is direct evidence of the entire developmental series of the crescent bodies in the bone-marrow.　The data furnished by recent investigation with regard to the development and the biological significance of these parasitic forms as the same concern the later stages of the development of the supposed *syzygies*, do not sustain the theory of multiplication by segmentation.　As first pointed out by Marchiafava and Celli, all authorities in spite of the many and conflicting opinions expressed as to the origin and the significance of the crescents, agree that the latter proceed from the small amœboid parasites, which multiply in the manner described by sporulation, parasites of æstivo-autumnal fever.　That the crescents are derived from parasites which do not sporulate with the described succession of forms, bodies with blocks of pigment, etc., but from crescents only, is a theory advanced by Grassi and Fletti alone.　They made of this a special genus, the " Laverania," and to the species which occurs in man they gave the name " *Laverania malaria*," in

contradistinction to the parasites causing grave fevers, to which they give the name *Hæmamœba præcox.*" From this it follows, therefore, that, according to these authorities, two species of two different genera are constituted by the various forms which we have described as comprising the two life-cycles of the same parasite, that is, the *pyretogeneous* and crescent cycle. After making systematic investigation in cases of æstival fever, by means of frequent punctures of the spleen, Bignami and Bastianelli gave forth their opposition to this view. They demonstrated that in all cases of this group, which are studied for a sufficiently long time without medical treatment, we can always follow the development of the parasite, on the one hand, up to the body with the central pigment and its fission, and on the other hand, up to the young endoglobular crescents. Apart from the fact that, by demonstrating the biological significance of the crescent bodies, more recent researches have absolutely excluded the theory once advocated by Grassi and Fletti, what we have just said, proves that the crescents are merely one phase in the life-history of the *æstivo-autumnal* parasite. It should not be forgotten that we often notice alteration in the crescent bodies, which must be held to be degenerative, and specially in preparation observed for sometimes. The process of vacuolisation of the ovoid, round, and crescent bodies can be plainly seen. For the most part, the parasitic body divides into numerous masses of unequal size, hyaline, and of simple outline, which gradually disappears within 15 to 20 minutes, or a little more, as if they were dissolved in the serum. By watching this process of disintegration, we become sure that the crescents have no membrane, because, if there were one, it ought to become apparent during this procedure. Several writers have described a segmentation (sporulation) of the semi-lunar bodies (even those who acknowledge that they never have seen this up to the present time, hold that a process of

multiplication must necessarily be present) ; and this, too, in addition to the above-mentioned degenerative alterations which certainly constitute the final phase of the crescents, if they do not reach the surroundings adapted to their further development, *viz.*, the mid-intestine of the mosquito. Two forms of segmentation of the crescents, one of fission scarcely begun, the other of complete fission, similar to what is seen in the segmentation cf the parasites of the regular fevers, are claimed to have been seen by Grassi and Fletti. Mannaberg describes a transverse segmentation, which usually occurs in the middle of the parasitic body, dividing the crescent into two equal parts. Canalis describes the sporulation of round bodies of semilunar origin, and even gives a drawing of it. Golgi held that in the crescents there was a process of internal differentiation, which led to the formation and to the emission of young parasites which invade new red blood corpuscles, hence occur renewed febrile attacks. It was upon the fact that the crescents persist in the blood during the apyretic interval separating a group of febrile paroxysms from the relapse, that those who held that there was a multiplication of the crescentic bodies, without being able to demonstrate it, based their belief ; and they held that the same could be explained only by a process of sporulation of the crescents themselves. Those who have described and pictured this sporulation, Canalis, for instance, described a sporulation in which the nucleus took no part at all, were evidently led into error by their preconceived notion, and mistook a generative process of disintegration for sporulation. It is believed, however, that the crescents do not multiply in the human blood ; for, as has been shown by Bignami and Bastianelli, the relapses of the fever are not in relation to the development of the crescent bodies, and further more, even under the best conditions of research, one does not succeed in finding a fission form of crescents, which could with certainty be held to be a sporulation. The so-called

flagellated bodies are the only developmental forms of the
crescents which can be studied in preparations of blood.
When such bodies are examined under the microscope, we
find that some of the crescents are motionless, or only show
change into ovoid or round bodies very slowly; others, as
soon as they have become round in shape, exhibit lively
movements of their pigmented granules, and suddenly shoot
out filaments of their pigment granules, the same are
endowed with great motility; in short, they turn into
flagellated forms. It is supposed that flagellation is a pheno-
menon which does not occur so long as the parasite remains
in the human blood; for the flagellated forms in question
are never seen immediately after the specimens are prepared,
but sometimes after the blood has been taken from the
circulation. The filaments or flagella start from the
periphery, either singly or at various points, or all together
from one point, and sometimes forming a bundle which
separates into two or three prolongations; and the so-called
flagellated body is made up of a pigmented hyaline body,
which is smaller than a red blood corpuscle. The flagella
are four or five times as long as the diameter of a red cell,
sometimes longer, and are usually pointed at their free
extremity, although they may be bulbous, or they may
present swelling along their continuity. Their motion is
continuous, or may be interrupted by pauses. Sometimes
they meet and rub each other, as do the feet of a fly; some-
times they whip the neighbouring red blood corpuscles, push
them about rapidly and change their shape, then they
become detached and move rapidly in the plasma, scatter-
ing the red corpuscles they meet. But sometimes their
motion gradually stops before they become detached; and
then, on careful observation, we find them, after a while
motionless and adherent to the pigmented body. During
the movements of the filaments the pigmented granules of
the parasitic body usually remain at the centre; but they

may be carried to the periphery, and even penetrate into the prolongations, which then appear to be canalised, where they exhibit rapid movements either in the direction of the free ends or backwards into the pigmented body again The movements of the pigmented granules within the pigmented body sometimes cease during the motion of the filaments ; but, again, they may continue for hours, even after the filaments have stopped moving and have become detached.   It is extremely rare in a fresh specimen to see a flagellated body in which the including red blood corpuscle is distinguishable, that is to say, a round body in which there are flagella which can be seen to be endoglobular ; but the fact that flagellated body is within a completely decolourised corpuscle is, in the case of a properly stained preparation, from the observation of, around the parasite, the shadowy outline of the red cell in question.   The movements cease, and all traces of the prolongations are lost, while the pigmented corpuscle remains distinctly visible, when we add a drop of distilled water to a specimen under the microscope in which there are bodies with flagella in active motion.   Nevertheless, the forms and the movements of the flagella are not in the least affected by a physiological solution of sodium chloride.   There are also other points to be noted in this connection ; for, in addition to the above, one may observe the emission of small, round, hyaline bodies which have become detached from the edges of many of the various forms of the crescent stage, that is to say, as well from the crescents as from the round or flagellated bodies.   This process has by some been described as that of *gemmation ;* and in it the little bodies become projected at the edges, and then detach themselves, and either move away from the parent body or remain close to it.   From one body of the crescent stage as many as two, three, or even five little bodies may thus make exit.   The emission of flagella, however, is not the end of all the actively motile

bodies of the crescent stage; for there have been described, by Marchiafava and Celli, special bodies with an undulatory movement of the contour. These bodies may be seen to revolve in one direction and then in another, while their peripheral portion is the seat of the most rapid undulatory motions; at the centre they have a pigmented nucleus which is either motionless, or seems to swing in correspondence with the peripheral oscillations. The movement of these bodies lasts from 20 to 40 minutes, when it slackens, becomes intermittent, and finally stops. It is necessary to examine preparations stained according to Romanowsky's method to acquire an exact idea of the structure of these bodies, and of the flagella especially, though all this may be seen in the ordinary fresh specimen. The flagellata of a hæmatazoan, found in the blood of young crows taken from their nests in malarial regions, were studied in this way by Sacharoff. He calls the same a phenomenon of degeneration, and describes the so-called flagella as *chromosomes* which have come out of the nucleus of the parasitic body, and flagellation as a process of perverted karyokinesis Using preparations in which the blood spread in the usual manner on the cover glass, and which was kept in a moist chamber for 10 or 20 minutes or more, and then rapidly dried in absolute alcohol for 25 or 30 minutes, Bignami and Bastianelli have more recently made use of the same method in the study of the structure of the flagellated bodies derived from the crescent. Under these circumstances, many of the crescents become flagellated (those that do not usually undergo changes presently to be described); indeed, Marshall, Ross, and Manson have demonstrated that a certain amount of moisture and exposure to the air favours this phenomenon. There is usually a certain amount of swelling to be seen in these preparations of the crescentic and round bodies; even the nuclear chromatin swells and takes on the form of granules, or blocks, or filaments. The

so-called bud is seen occasionally, that is to say, when some minute chromatin masses make their exit from the parasitic body and adhere to the periphery of the latter. We usually find four for each body, rarely more, in stained specimens in which the number of flagella can be accurately observed. The flagellata themselves are made up of a pigmented body, which takes on a blue stain, and in which the chromatin is divided into blocks arranged along the periphery ; from these the peripheral *chromosomes* project filaments which, surrounded by a very thin layer of protoplasm, constitute the individual flagella. In cases in which we see an isolated motile fila-ment or flagellum, one which is completely formed, we find that the chromatin tends to be massed at the centre, the extremities being formed of protoplasm ; the chromatin may also occur in the form of a series of granules or rods instead of filaments. The morphological characteristics mentioned above are not, however, possessed by all the flagellata ; for there are some in which the filaments do not contain any chromatin, but are composed of protoplasm alone, and others in which there may be one or two filaments provided with chromatin, the others being formed of protoplasm. Such forms are to be considered as incomplete, that is to say, as flagellata whose development has been interrupted by desic-cation. In fact, it is in the place where it naturally occurs, that is to say, in the mid-intestine of the anopheles, that these forms, as well as some others or irregular aspects are to be found, being never seen in the moist chamber or at all when the process of flagellation is completed. Character-istics, differing somewhat from those of the bodies which give origin to filaments, are exhibited by crescents which do not become flagellated when kept in the moist chamber under the same conditions as the others. The swell, and their cytoplasm takes on a deeper blue stain, the chromatin is in smaller amount, and is gathered in granules and rods in the nucleus, which is either central or subcentral or surrounded

by a wreath of pigment ; but, as a rule, a certain number of granules of chromatin, which constitute the so-called buds, which may be found at the periphery of the flagellated bodies and can be seen in fresh preparations, are to be seen to have made their exit from the nucleus, and to be adherent to the periphery of the protoplasm.   Those which become flagellated, and others which do not and which differ from the first in some minor morphological details are the two classes of crescent bodies which we must therefore recognise.   It may here be noted that many different theories have been advanced as to the biological significance of the crescents, as well as that of the bodies derived from them. Some of these we can dismiss at once, taking note only of the facts demonstrated regarding structure.   It is easy to do away with the idea that they are bodies capable of multiply-ing in the human blood, as was held by some who reasoned by analogy rather than from established facts, and also by Golgi, Antolessi, Canalis, Grassi and Fletti.   In like manner it is contrary to reason to admit that they are cystic bodies, as Laveran and Mannaberg believed, since it has now been proved that they have no membrane. Nor is it to be admitted that they are resistant spores, as was believed by Councilman, who was struck by the resistance opposed by these forms to quinine, and this because of what has been learnt in regard to their biological properties, and because of the fact already described in relation to their ultimate development.   The hypothesis that the crescents are sterile bodies is one usually opposed to these views.   Bignami considered the crescents to be form of divergent and interrupted develop-ment of the æstivo-autumnal parasites ; the said forms of divergent development, because following the life-phase of the parasites, he thought, he observed that, at a certain point in their growth, while some were preparing to multiply, others deviated from their course, and, without multiplying, continued to increase in size until they formed typical

crescents ; he added forms of interrupted development because, at a given moment, these forms, without multiplying, degenerated in various ways and disappeared in the blood. The same theory was taken up later by Bignami and Bastianelli, who undertook the systematic study of peripheral and of spleenic blood from patients suffering from primary æstivo-autumnal feveis, with the view of ascertaining the time in the course of the disease at which the first crescents appeared, how long they persisted in the blood, what was their relation to relapses, etc. Furthermore, it was ascertained by these researches that no crescents were ever seen to multiply, and that they could not be held to be the cause of relapses : these writers held that they were the sterile forms of the *æstivo-autumnal* parasite. In 1894 they endeavoured to explain the sterility of these bodies by the theory that the crescents have the same biological significance as the forms belonging to several other parasites which complete their life-cycle outside the organism in which they are found. They affirmed, it is a well-known fact, that the two cycles of development have been demonstrated in several endocellular parasites belonging to the group of the coccidia ; one cycle of development is completed exclusively during the parasitic life ; but after the parasite has lived as such during a series of generations, there begins a second life-cycle, represented by forms which can terminate their development only in the surrounding atmosphere or in the tissues of some other animal ; should these forms of the second cycle not make their exit from the body of the animal in which they started, they remained sterile, and after a while degenerate and die. These writers then believed that the crescents were sterile forms in man and for man ; and this view is the exact statement of a fact which has now been established, if the observation be limited to what occurs in human blood, as was the case until comparatively recent. A full solution of the biological significance of these forms has been arrived at ;

for the fact that the crescents reached the tissues of another animal, *i.e.*, the mid-intestine of the mosquito, and there complete their life-cycle, has been shown by the most modern researches.   Various theories have been advanced as to the significance of the so-called flagellata.   The final and perfected phase of the malarial parasite was what Laveran considered his motile filaments to be ; but these same structures were looked upon by Marchiafava and Celli as protoplasmic prolongations of the pigmented bodies, having the significance of flagella   and they regarded the flagellated bodies as representing a later stage of development of the pigmented plasmodia.   On the other hand, Grassi and Fletti held that the so-called flagellata were merely a product of the degeneration and destruction of the adult parasites.   These theories have, of course, been demolished by modern researches regarding the structure of these bodies, as has also been the opinion of Labbe, who likewise considers them to be the forms of death, not found in the living organism, but outside of it only, a product of the physiochemical action which modifies the plasma and the corpuscles which are withdrawn from the blood-vessels.   The opinion that the flagellated bodies represent the first principle of an extra-human phase of life, which dies from lack of a suitable soil, has been expressed by Mannaberg, who also affirms that, if these were forms of death, there would be no explanation of the facts that they are seen only in a limited number of parasites. The   theory   that the flagella are pre-formed within the crescents and the round body, from which they make their exit when both the crescent and the round bodies are outside the human organism, has been advanced by Manson.   He has also endeavoured to demonstrate, by staining with carbolised fuchsin, the presence of the filaments pre-formed within a delicate cyst.   According to this theory, the flagellum is a special form of spore, which is developed only in the outer air, "in the interest of the extracorporeal life of the parasite,"

the seat of this ulterior development the body of a suctorial insect, specifically the mosquito. This theory has not been sustained by later researches. In fact, a study of the structure has shown that the flagella are not pre-formed in the crescents and the round bodies; within these we find the filaments of chromation which go to make part of the flagella, but not to form them in their entirety. That the pigmented bodies, and not the non-pigmented flagella, are developed in the mosquito, has finally been demonstrated by the researches of Ross, upon the *proteosoma* of birds, as well as by those carried on in Rome upon the malarial parasite in man. There seems now every reason to believe that the crescents and the flagellata are sexual forms of the malarial parasite; and that a new being, which begins its existence in the tissues of the mosquito, is produced by a reproductive act, in which the flagellum represents the male element and an adult crescent the female cell. This theory has been founded, in the first place, upon the sexual phenomena which occur in various *sporozoa*. Simond was the first to propound the theory that the flagellata of malaria are sexual forms. He studies the life-phases of *coccidium oviforme*, of *cariophagus salamandræ*, etc., and found in these parasites two cycles; firstly, a cycle which he called *asporulate*, which is completed in the host, and gives rise to the formation of *falciform* corpuscles, *merozoites;* and, secondly, a sporulate cycle, represented by the encysted forms, which is completed outside the host, insuring the life of the coccidium in its new surroundings. Now, this second cycle begins by an act of fecundation, the male element being represented by an adult form in which the nuclear chromatin is divided into a large number of filaments, which separate and go to the periphery of the parasitic body, from which they emerge and remain for a while adherent to its edges like the horse's mane and then detach themselves, being surrounded by a thin layer of protoplasm. In fresh specimens this process occurs with

so great rapidity in movement that the bodies appear to be flagellated. The filaments are *spermatozoa* which fecundate the young coccidia, and these then begin the sporulation cycle, or the cycle by which is assured the conservation of the species outside the host, and the possibility of fresh infections. Our author, these facts being established, expresses it as his opinion that the polymitus of Danilewsky and the flagellata of malaria have the same functions as the *pseudo-flagellata* of the coccidia, as well as the same significance as the latter. During the time that they were investigating the development of the *Adelea ovata* and the *Eimeria Schneiderei, Schaudinn* and *Siedlecki* were able to follow, in the most complete manner, the development of the sexual forms and fecundation ; they describe the accompanying nuclear modifications (the latter observer later, in 1898, studied similar phenomena in another coccidium). Applying zoological nomenclature to the coccidia, they call the sexual forms, in general, *gametes*, the female elements *macrogametes*, the cells producing the male element *microgametocytes*, and the male elements *microgametes*. MacCallum tried to discover whether sexual forms and phenomena of copulation were to be found in some hæmatozoa, and succeeded in witnessing, under the microscope, the act of fecundation in the Halteridium of birds. He divides the adult forms of the Halteridium into granular forms, and forms of a homogeneous hyaline aspect, the latter only becoming flagellated. A flagellum penetrates into a granular adult form, which, after fecundation, becomes changed into a motile body resembling the so-called *vermiculus Danilewsky*. The penetration of a flagellum, into a round body of crescent origin was twice seen by him whilst studying a case of æstivo-autumnal fever in man, in which there were many crescent forms. Indeed, the theory of fecundation must be considered as the most consonant with the latest knowledge in regard to the biology of the sporozoa ; in the latter it would seem that the sexual

phenomena are constant, and that the formation of the encyst-
ed forms, which begin the cycle that is continued outside of the
body, is preceded by the sexual act. That the forms which
pass from man to the mosquito are sexual forms, and also
that an act of fecundation initiates the new life-cycle in the
middle intestine of the insect, may therefore, and reasoning
from analogy, be taken as in the highest degree probable.
In support of this theory may be the comparatively recent
researches of Bastianelli and Bignami, according to which
by the use of Romanowsky's staining process, we find two
kinds of crescentic bodies, differing in the amount of their
chromatin, which is greater in the forms which become
flagellated, and in the staining of the cytoplasm, which in
the non-flagellated forms is of a much deeper shade of blue.
The female elements, or the bodies which do not become
flagellated, are usually now called the *macrogametes;* the
crescent bodies are termed the *gametes;* those which become
flagellated, or the male elements, are known as the *microga-
metocytes;* and the individual flagella are designated the
microgameres, after Schaudinn and Siedlecki, who have studied
the sexual forms of the sporozoa. The new life-cycle which
is completed within the tissues of the mosquito, begins with
these phenomena, whose seat is naturally not the outer world,
where they were at first chiefly observed, but the middle
intestine of some species of the insect in question. The fact
that all these parasitic forms consist of a nuclear formation,
whose constituent parts are not seen with equal clearness
in all the various stages of their existence, and of cytoplasm,
would appear from the above description. It is important
to remember this at the very outset of the study of the
general morphological and biological properties of the
æstivo-autumnal parasites. Regarding the nuclear forma-
tion, all that we see in the very young forms is the
chromatin globule ; and to this various writers have given
different names. Mannaberg and others called it the *nucleolus,*

Grassi and Fletti the *nucleoliform node*, whilst most authorities preferred, as a rule, to designate it as the small body of chromatin in order to avoid cytological discussion. Similar bodies have been described in many lower organisms ; as, for instance, in the coccidia. Some writers, following Labbe, call them *Karyosomata*, others, such as Rhumbler, call them *Binnenkörper* (while some, in view of more recent researches, apparently are not the same as the nucleoli of the cells of the higher organism) in order to adopt an indifferent name. In some coccidia these small inner bodies, or Binnenkörper, can be distinguished from the nuclear chromatin, which is arranged in threads and granules; and we can see what becomes of each during the process of division, as Schaudinn and Siedlecki did in the case of *Adelea ovata*. A clear distinction between the nucleus and the nuclear chromatin is not, in the case of the æstivo-autumnal parasite, permitted by the various technical methods at our disposal. A light zone, which is supposed to be nuclear juice and which is not apparent in the forms that are very young, is seen in bodies, which are in the course of development, around this chromatin body. Many writers affirm that the nuclear membrane circumscribes the clear zones. It can, however, only be demonstrated in the adult bodies of the second cycle. *i.e.*, in the crescent. We can only assume the probability of its presence, firstly, by the distinctness with which the nuclear formation is seen to be separated from the cytoplasm; and secondly, by analogy with what is known as to similar organism, whose structure, because of their greater size, can be more easily studied : for by none of the methods in use can we find it with any certainty in the young and in the developing forms, and even less in those undergoing multiplication. The contents of the cells, the protoplasm or cytoplasm, as already mentioned, becomes pigmented at the periphery ; but, in the case of crescents, we find the pigments gathered in the innermost portion of

the cytoplasm, immediately surrounding the nuclear forma-
tion. It has been described as a vacuole, which is almost
constant in the very young forms, and which disappears in
the course of their development. That its presence is the
case of the annular forms assumed by the plasmodia in
fresh preparations, and of the appearance which these take
on in preparations stained according to Romanowsky's
method (in which they are seen as thin blue lines, in which,
while the central portion, or vacuole, is pale or colourless,
the chromatin body is seen of a purplish-red colour), is the
opinion held by the majority of observers. We have also
noted the fact that, in the case of the young forms, the pheno-
mena of motion is very lively, and that this same diminishes
by degrees, to cease entirely during the stage of multipli-
cation. These movements concern the protoplasm ; but it is
probable that the nucleus also has amœboid movements.
Except such as accompany the formation and extrusion of
the motile filaments, in the crescent cycle we have no move-
ments. It is by the successive division of the nuclear
chromatin, rudimentary form of *karyokinesis*, within an
adventitious cyst formed by the red blood corpuscle, that
multiplication occurs. These little bodies resulting from the
division are not provided with a membrane ; they have been
called *spores* or *gymnospores*, and the process of their form-
ation *sporulation*, because these expressions are in current
use amongst naturalists to indicate multiplication by
segmentation in similar organism. It is to be remembered,
however, that the meaning is not the same at all as tha of a
spore in bacteriology. In fact, these spores of the malarial
parasite have none of the biological properties of the enduring
spores of bacteria, that is to say, they are not endowed with
special powers of resistance ; and, as regards their structures,
as has been said, they do not differ in any essential points
from the young *plasmodia*. Bastianelli and Bignami have
suggested that some spores which were born naked might,

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under special conditions, acquire a membrane and lose their
capacity for staining; but this is a theory put forth in
explanation of cases, a few, in which, during a latent infection,
it has not been possible to find, even in the spleen, any
parasites to the presence of which could be referred the
occurrence of a late relapse. Furthermore, proof of this
theory has not yet been forthcoming. Antolessi held that
the spores of malarial parasites were provided with a mem-
brane, *clamidospores*, but this view has not been confirmed
by more recent researches. The red blood corpuscles are
the seat of the development of the æstivo-autumnal parasites
just as they are of the others   Laveran thought that the
parasites were free in the blood, but, later on, Marchiafava
and Celli, who also noted that in certain cases, plasmodia
were only partially enclosed in the red blood corpuscles, as
though they were about to leave them, held that the plasmodia
were endoglobular ; this view being based upon the fact that
their *pseudopodia* never went beyond the boundary of the
red cells   Furthermore, the amœboid bodies are seen as if
floating in the protoplasm of the corpuscles, becoming less
visible, or, as it were, submerged, and then re-appearing, one
or two prolongations first becoming visible, and then the
entire body. Although he still believed in the position of
the adult bodies being endoglobular, Mannaberg ultimately
expressed his doubt as to whether the young plasmodia—the
non-pigmented plasmodia of Marchiafava and Celli—were
within the red blood corpuscles.   He says that a direct proof
that some forms are endoglobular is found in the observation
of the spherical bodies of the crescent stage, or the large
tertian bodies, at the moment when they are leaving the red
corpuscles, for it is possible to doubt that they make their
exit by the bursting open of the corpuscle itself. But the
small non-pigmented form, according to him, long remains
simply adherent to the globules. He says that it is very
difficult to determine whether a parasite is within a corpuscle

or simply adherent to it, or, as it were, pressed into its
surface ; in the latter case, it might be that the pseudopodia
were unable to go beyond the limits of the corpuscles, as
noted by Marchiafava and Celli, simply by the fact of
their viscidity which might prevent them from becoming
detached from the cells He affirms that there is a
sort of depression in the corpuscle which contains them.
Such depression, with distinct edges, on the surface of
the corpuscle, according to him, can be seen by means
of oblique illumination and an open diaphragm, allowing
of the examination of the bodies in relief. The endoglo-
bular nature of the vast majority of the parasites, even
the young non-pigmented forms, however, is believed in,
none the less, in spite of all this. Specially it is worth
noting that, if we once admit the endoglobular situation of
the development and the adult forms, the question loses all its
interest, and there remains simply for us to ascertain at what
period of their development the young parasites enter into
the substance of the red blood corpuscle. It is now gener-
ally held that the theory that the majority of the young
forms are endoglobular is demonstrated by the fact, which
has already been considered, that by following their motions,
we can see them apparently becoming submerged in the
substance of the corpuscles, and then emerge from it again
Furthermore, in the cadaver, in which the parasites have
lost their amœboid qualities, we sometimes see them moving
in toto, with a floating motion, within the corpuscle, as
though the contents of the red blood cell were liquefying.
That the globule is transformed into a little bladder full
of fluid, in which the parasite is seen to oscillate if the
corpuscle is moved, is the impression received. We have
already dwelt upon the fact that the young parasite some-
times seems to be embedded or pressed into the surface
of the corpuscle ; but forms, which are at the beginning
of pigmented stage, are scarcely ever seen in this position,

but are always endoglobular.   From this it is evident that after remaining for a short time adherent to the red corpuscle the young plasmodia penetrate within its substance; and this occurrence is essential to their further development. Though the latter is in site endoglobular, that there is an equal distribution of parasites throughout the vascular system does not follow therefrom.   The mechanical condition of the circulation differs in the various viscera, and moreover, as each viscus modifies in a special manner, the blood which circulates in it, the conditions of development for the parasite must differ in the various organs. It is an interesting fact that the parasites in their several life-phases, while still endoglobular may have a predilection for certain situations. Thus the young forms of *pyretogenous* cycle circulate in the blood, while the adult forms, bodies undergoing multiplication, and fission forms, as a rule, remain stationary in the internal viscera.   This may partly be due to the alterations produced in the corpuscle as the parasite develops, but it is partly and chiefly, owing to a special biological property of the æstivo-autumnal parasite. The bodies of the crescent group behave differently, the young ones being founded only within the vessels of the viscera, and are chiefly, if not exclusively, formed in the bone-marrow, while the adult form enters the general circulation.   The adult crescents are the bodies which, when taken with the blood by the mosquito, continue their development in the intestine of this insect, and, therefore, they have just so much more chance of completing their life-cycle if they circulate in the blood for several days.   In short, we must see in these facts a phenomenon of adaptation.   Before leaving this subject we must consider for a while the parasites which complete their entire life-cycle without becoming pigmented.

The theory that this represented the multiplication of these plasmodia was, in 1885, suggested by Marchiafava and Celli.   They described small endoglobular fission

forms that did not show the smallest trace of pigment ; and drew attention to the fact that the fission in question of the plasmodia may occur even before the red , blood corpuscle in which they have developed, are entirely destroyed. They stained sections of the cerebral cortex with *vesuvin*, in some cases of pernicious fever, and found that the capillaries were overfilled with red corpuscles, many of which contained parasites in all stages of development, all of which were non-pigmented ; these were forms already divided into small clumps of ovoid bodies all of equal size (staining like the so-called spores of the malarial parasite, and sometimes arranged in rosette forms), young discoid forms, and forms in process of division. These authors concluded from this that there are malarial parasites which may complete their whole cycle of development without becoming pigmented, and believed that there may be an absence of melanæmia in certain cases of malaria. Bignami (who studied the parasites in a larger number of cases of pernicious fever), Marchoux (who studied the malaria of Senegal, and Smith and Kilborn (who found in the Texas fever of cattle, as did also Dionisi in bats, etc., endoglobular parasites which completed their whole life-cycle without producing pigment), as well as others, have confirmed these data. As far as pernicious fevers, at least, are concerned, it must not be forgotten that for these researches we can make use only of fresh specimens, or of those which have been preserved in alcohol for a short time only. We know, in fact, that the pigment may gradually disappear altogether from the brains kept for a long time in alcohol ; so that, when we find in them non-pigmented fission forms, we cannot be sure that the loss of pigment is not artificial. Furthermore, until the complete absence of melanin has been demonstrated by repeated punctures of the spleen, we can never be certain of the existence of an infection without melanæmia. It is only in the absence of black pigment that the forms

in process of development differ from the ordinary æstivo-
autumnal parasites ; and, for the most part, rarely more than
eight to ten spores are to be seen in the fission forms with-
out pigment. The question has been raised as to whether
these forms represent a definite parasitic species, or whether
they are æstivo-autumnal parasites, which, before the pigment
has formed, have undergone a process of premature multipli-
cation. Some writers support the first opinion ; thus,
Mannaberg speaks of a *quotidian* due to a parasite which does
not produce pigment. Until further discoveries are forth-
coming, it is, however, inadvisable to dogmatise on this
point ; for, in cases in which some have found non-pigmented
fission forms, there have always been pigmented parasites
as well. It is also noteworthy that the usual fission forms
have been found in the spleen with blocks of pigments,
though in the vessels of such an organ as the brain, all the
parasites in every stage of development might be non-
pigmented—the complete life-cycle being under observation.
A pure culture of the non-pigmented parasites has not, so
far as I am aware, been up to the present time forthcoming,
that is to say, we have no example of a well-studied case
in man, in which all the parasites in the vessels of all the
viscera are without pigment. However, in view of the fact
that they have been found only in tropical or in pernicious
fevers, and that they are always found in company with
parasitic forms that could be diagnosed with absolute
certainty as *æstivo-autumnal*, it is believed that these
forms may be considered as related to the *organisms* of the
summer-autumn fever.

CHAPTER X.

LIFE-CYCLE OF THE MALARIAL PARASITE IN THE MOSQUITO.

The behaviour of the malarial parasite in mosquitoes has attracted considerable attention ; and much has been published from time to time regarding the procedure of the research instituted. Some experimenters have tried to gain information on the conduct of the parasite outside the body of man by starting from the known forms in that personage'; whereas others have sought for them directly in the air, the dew, or the water of marshes. The object of the first was to cultivate the human parasites in various *culture media,* modifying in various ways the ordinary media used in the study of bacteria. This was the procedure of Marchiafava and Celli in their earliest experiments. The second class of investigators searched in the atmosphere, and in marsh water for free living organism resembling the parasite in man : this was done by Laveran, who speaks of finding motile filament in water, similar to those in malarial blood. Others, as Silvestrini, injected the washings from malarial earth (Celli and Sanfelici did similarly in the case of birds), marsh, water, etc., under the skin, in order to ascertain whether they could in this manner produce a malarial disease. Grassi and Calandraccio for a while thought that they had found the malarial parasite existing freely in the earth. But the failure of all these experiments caused several investigators to think that their researches must be turned in other directions in order to solve the problem, and that possibly the plasmodia were to be found as parasites in other animals, and not in the free state outside the body of man. The intimate relation between malaria and certain insects is, indeed, a popular belief in several malarial districts. Now, since the theory has been proved to be a

fact, various authors have endeavoured to find in the earlier writers the first allusion to this allegation. At the beginning of the 18th century, Lancisi, who actively upheld a theory of a close relation between malarial fever and *marshes*, attributed to the *effluvia* of the latter their injurious effects upon man. He appears to have attached importance to everything which, originating from stagnant waters, can in any way attack man, including mosquitoes, to which he pays particular attention, noting their abundance in marshy regions, and above all the abundance of the vermiculi, " whose transfoi mation he noticed in *Sti idulos culices*," and other insects. He assumes that there may be several ways in which these insects may have an injurious influence upon the inhabitants of malarious localities. He expresses the suspicion that the injurious action may be due to the ingestion of waters rendered foul by the insects ; but, what is of more interest, he also admits that they may do more harm by their stings not simply by stinging, but by the injection of a toxic substance in the act of puncturing the skin. He adds that the insects—the " *animated effluvia of marshes* "— may vitiate our systems not only by the effects of the local irrigation, but by the liquid which they leave behind after their sting. Besides this water, others since his time have mentioned a cautious attitude on the question, admitting that the vehicles of infection might be many, and that the parasite may be found in both the earth and water of marshy localities, and might be communicated to man through the ingestion of infected water. This was the attitude of Laveran, who, in contradistinction to Lancisi in the previous century, did not even hint at the possibility of inoculation, but who, with him, held that man can be infected in various ways. He searched for the parasites in water, which he considers to be the chief, if not the only, vehicle of infection ; and as to the mosquitoes, he propounded the theory that they may take the parasite from man and then infect water, as

they do in the case of filaria.   Since, taking into considera-
tion the condition of knowledge at the time of its inception,
and when demonstrative facts are sought, no hypothesis can
properly be called scientific, unless it is sustained by a
sufficient number of arrangements to give it some proba-
bility, it is only within the most recent years that the mos-
quito theory can be said to have really entered the realm of
scientific discussion.   There are at the present time two ways
in which investigations are pursued, those of Bignami and
Manson.   It was the first-mentioned observer who, endeavour-
ing to ascertain how fevers are taken, showed how great are
the difficulties met with in considering the air and water as
vehicles, demonstrated the probability of inoculation by the
mosquito, dwelling upon the analogy of human malaria with
Texas fever; furthermore, since 1894, he has endeavoured
to prove these views by experimental demonstration.   The
other method has been followed by Manson, who, taking
up Laveran's theory, tried to find out what were the forms of
human parasites which were capable of passing into mos-
quitoes and there continuing their development.   He consi-
dered the flagella to be spores, which becoming free in the
mosquito's intestines from the cysts containing them, con-
tinued to develop, and at the death of the mosquito became
free in the water, which was thus converted into a vehicle
of infection to man   These two theories seemed at first to
be so absolutely contradictory that they gave rise to written
discussion, which have certainly been of use in stimulating
the study of the subject.   Special subjects of discussion were
the significance attributed by Manson to the flagella, which
is not upheld by fact, and the importance attributed to the
Laveran and Manson theory of water as a vehicle of
infection which is contradicted by accurate epidemiological
observations, as well as by actual experiment.   By demon-
strating the fact that mosquitoes take the parasite from
man and inoculate man with it again, further research

has led to a harmony in fundamental opinions. Manson's theory had the great merit in serving as a guide to the researches of Ross, who, by causing birds infected with *proteosoma* (Labbe) to be stung by a species of mosquito (gray mosquito), determined in the latter the forms of a new parasitic life-cycle. These were found in the walls of the middle intestine where. according to Ross, the proteosoma assumes the aspect of a coccidium (*proteosoma coccidia*) ; in the mature capsules of these coccidia were formed germinal corpuscles (germinal rods), which accumulated in the poison-salivary glands of the gray mosquito, healthy sparrows being capable of becoming infected with the proteosoma at this point. The important fact that not every species of mosquito can give lodgment to a given *hæmatozoön* (in fact, Ross found the developmental stages of his proteosoma coccidia only in the gray mosquito) has been forthcoming from these researches, which gave us our first information upon the life-forms of a *hæmosporidium* in the body of a mosquito. That only a determined species of mosquito can transport the infection to man was rendered more probable than ever by the same ; whence the necessity of a preliminary zoological study upon mosquitoes of malarial regions, with the view of ascertaining the dominant species. With this idea Grassi, investigating the distribution of mosquitoes in malarial regions, in the summer of 1898, came to the conclusion, that in malarial countries, in addition to the species found in non-malarial regions, there are others which are completely absent from the latter places. In malarial regions we find in large numbers the *Anopheles claviger*, other species of Anopheles, the *Culex penicellaris*, and other species of Culex which must naturally be open to suspicion if the mosquito theory of the origin of human malarial be once admitted. In non-malarial countries the *Culex pipiens* and other species of Culex predominate. These points were now fully investigated. With these species Bignami obtained in Rome the first case of

experimental malaria in man, this being reported in 1898 (November).   In rapid succession there followed the observations of Bignami and Bastianelli, upon the development of human parasites in mosquitoes of the genus Anopheles and specially in Anopheles claviger, which was the chief one to attract the attention of these observers, because of its abundance in the Roman Campagna and of Grassi.   These observers have shown that the parasites of human malaria pursue in the Anopheles a life-cycle resembling that described by Ross in the case of the proteosoma in birds.

THE STUDY OF MALARIAL MOSQUITO.

From the foregoing remarks it will be evident that the malarial parasites of man can be entertained by only determined species of mosquitoes.   It is necessary, then, to prescribe this class of insect, that is to say, the genus Anopheles. Palpi are present in both sexes about as large as the proboscis.   The palpi in the female are four-jointed, but in the basal joint there is a constriction towards the root, which apparently forms a basal articulation, and gives the pulpus the appearance of being five-jointed ; another constriction sometimes makes it six-jointed.   The palpi of the male are really three-jointed, but appear four-jointed by reason of a constriction in the basal portion towards the root ; and sometimes the presence of two constrictions, one towards the middle of the long portion and one in the apparent basal joint, gives the appearance of five or six articulations.   The appearance of five joints in the female and four in the male is the usual one.   In the female the palpi resemble straight filaments, which in repose are parallel with the proboscis, forming with it a bundle of three parts : when the female stings, they rise and diverge ; in the female the *antepenultimate* joints is as long as, or longer than, both the *penultimate* and *ultimate*. In the male the palpi in the last two joints are short, thick and olive-shaped   The *nucha* has a posterior crown of

scales. The legs are very long, ending in simple or dentated *claws* or in *ungues*. The abdomen is *pilose* on both its dorsal and ventral surfaces, but there are no squamæ, which are abundant in the genus Culex. Five species of Anopheles are to be found in Europe, which, according as to whether or not the wings are spotted, are divided into two groups : those without spots but possessed of wings include the *Anopheles byfurcatus*, the *Anopheles villosus* and the *Anopheles nigripes*. The *Anopheles bifurcatus* have wings without spots. This species is less black than the following, and of medium size. It is much less abundant than the *Anopheles claviger* in the Roman Campagna. Some individuals may be smaller and brownish-black, some larger and brownish-yellow The *Anopheles villosus* resembles the bifurcatus (Ficalbi thinks that possibly it may simply be a variety of this and not a species at all), but is larger and more pilose Ficalbi thinks that the *Anopheles nigripes*, instead of constituting a distinct species, may be a small and dark specimen of bifurcatus, which he has had frequent opportunities of observing. It has wings without spots, like the preceding; also a proboscis, palpi, tibiæ, and tarsi blacker than in the *Anopheles bifurcatus;* and it is not more than 8 mm., that is to say, it is smaller in size. He says that it belongs to Northern Europe, and is rare. In the category of spotted wings we have the *Anopheles claviger* and the *Anopheles pictus.* The former is also termed the *Anopheles maculipennis*, and has wings with four spots formed by masses of *chitinous* squamæ. Femora of the anterior pair are not enlarged at the base. With the exception that the *Anopheles claviger* has the spotted wings and is in appearance somewhat more yellowish, the description of the *Anopheles claviger* agrees with that of the *Anopheles bifurcatus.* The wings are brown, specially in the female, or slightly yellowish-brown ; and the total length of the body, including the proboscis, of the female is 7·5 to 9 mm., the female being always *larger*

than the male.   Even with the naked eye, we can distinctly
see the four black spots, which are, as a rule, more conspi-
cuous and better developed in the female than in the male,
and are so placed that, if joined by an imaginary line, they
would form a capital L.   Under the magnifying glass we see
that the wings are rich in black scales, an accumulation of
which produces the spots.   It is in well-watered plains that
this species is so abundant ; and it appears to be disseminated
throughout Europe, being found in England, Scandinavia,
Austria, Germany, Russia, etc.   It is largely disseminated in
Italy where it is the most common species of the genus Ano-
pheles, and is commonly called the *zanzarone* or big mosquito.
Regarding the *Anopheles pictus*, we may note that the wings,
even to the naked eye, seem to have blackish-brown and
rather tawny light yellowish spots, due to the accumulation
of squamæ of these colours.   In the proximal third the
femora of the anterior pair are slightly enlarged.   The
anterior margins of the wings, as far as their tips, are of a
blackish-brown colour, which is interrupted by three yellow-
ish marginal spots.   The central coloured spot is the
largest, the posterior the smallest, the latter not touching
the margin of the wing.   Five or six brownish spots, some-
times seven, are produced in the remaining portion of the
wings, by the black squamæ of nervation accumulating at
certain points, and alternating with yellow squamæ.   There
are black scales on the posterior margin of the wings ; and
these, at a point corresponding to the anterior third of the
margin, are of a tawny lightest yellow colour, forming
marginal spots of that hue.   From 7 to 8 mm. would be the
measurement of the body of the female, including the
proboscis.   Only males of this species were caught by Loew
on the coasts of Asia Minor, opposite the island of Rhodes ;
and he thought them indigenous to Southern Europe.   In the
summer time, Ficalbi captured only females of this species
in Tuscany in the forest of Tombolo near Pisa.   As seen

by the study of the specimen sent by Ross to Grassi in Rome, the mosquitoes with spotted wings, upon which Ross experimented in this country, belong to the genus *Anopheles* and are very similar to, if not identical with, the *Anopheles pictus*. Ross distinguishes two varieties, small and large, *dappled-winged* musquitoes. In Italy also there are small and large ones that Grassi regards as different species of Anopheles, distinguishing them not only by their dimensions, but also by the designs on wings and palpi. Grassi calls the large variety, found in Italy, the *Anopheles pseudopictus;* and it is about 11 mm. in its entire length. The *Anopheles pictus*, mentioned above, corresponds to the small form. Very little appears to be known regarding the life and habits of this species of mosquito. The facts observed in the Roman Campagna within recent years refer almost exclusively to the *Anopheles claviger*, to which appears to belong the chief rôle in the transmission of malaria, at least in such regions. It is the most common and the most numerous of the genus *Anopheles* in localities of grave malaria therein. In fact, the development of all the three varieties of the malarial parasite of man has been observed in this species of mosquito. In addition to the *Anopheles*, we find in the fields, during the spring and summer and autumn, many kinds of mosquito belonging to the genus Culex But, as the season advances, specially when the temperature begins to be lowered, the *Anopheles claviger* begins to predominate in the houses, huts, and stables. This is because, with the first advent of cold weather, the fecundated females prepare to hibernate, as nearly all mosquitoes do, and take refuge in an enclosed place where there are animals and men ; these hibernating females awake, very lively, and sting as usual, when gathered up and take to laboratories with a temperature of about 68° F. Where the winter season is mild, as on the coast of Southern Italy, we find females of the *Anopheles claviger*. hibernating

in caves. The males disappear, and it is evident that only the fertile females hibernate. In the winter the females of *Anopheles pictus* are to be found in caves in Southern Italy; and they do not appear to hibernate in houses. It is in grottos, in the trunks of trees, under bushes, etc., that the species of the genus Culex, *e.g.*, Culex pipiens appear by preference to perform this act. Now, as soon as the warm weather arrives, the females fly about and sting as usual, and then lay their eggs. Females transported to the laboratory, and kept at a temperature of between 68° and 71° F. laid eggs, as witnessed by Bastianelli and Bignami, in the month of March; the larvæ were seen a few days later, and developed in from 15 to 20 days. The insect remained in the chrysalis stage for four to five days; thus, after about 25 to 30 days in all, the insect emerged from the puparium. The females were seen to have the power of biting and drawing blood in from four to five days after they were born.

It is not a difficult matter to distinguish the eggs from those of the *Culex pipiens;* they are shaped like an elongated spindle with two lateral wings and are deposited in strings. In each string the individual eggs are placed transversely, and touch each other in the direction of the long axis; they do not therefore have the heaped-up appearance of the Culex pipiens.

The larvæ are also easily distinguished from those of the Culex pipiens; for they are brown, very agile, and always move in a *horizontal* direction, never in a *vertical* or oblique one, as do those of the Culex pipiens. They live in stagnant, preferably in deep water; and, if the surface of the water be even slightly agitated, they take refuge at the bottom. They are usually found isolated or in small groups, not gathered into large masses like the larvæ of the Culex pipiens. They have been seen existing and developing perfectly in very dirty stagnant waters, swarming with every kind of insect-life, though Ficalbi affirms that they do not choose

such dirty waters as those of the Cluex frequently do, but often live in clear water. Herbs supply food for the males, but the females suck blood, and are exceedingly voracious. While we can rearly make an individual of the genus Culex bite by enclosing it in a glass tube, the open end of which is in contact with the human skin, the female of *Anopheles claviger* is easily induced to bite under these conditions. They swarm in stables, and attack domestic animals, preferably the horse   Though some rare individuals appear never to bite, in the case of many members the bite in certain persons produces persistent wheal which causes the most troublesome itching ; but in others, however, the bite leaves no trace at all.   They live in the country chiefly, through sometimes they are found in suburban localities.   They prefer places where there is plenty of water, and are seldom or never to be found hibernating inside of houses, though they may swarm in the adjoining gardens.   The isolated cases of 'malaria which sometimes are seen to occur in healthy localities may perhaps be explained by the transformation of hay, etc., from unhealthy to healthy localities or towns.   The question of their migration is still undecided in other respects.   After hibernation the fecundated females seek water, and there deposit their eggs, so that in the spring there are new generations of winged insects   These, during the hot season, may give rise to several generations.   *   *   *

In order to study the development of the malarial parasites of the mosquito, it is necessary to cause adult patients to be bitten by these insects enclosed in glass tubes, the mouths of which are applied to the skin until the enclosed insects have become satisfied.   They can then be set free, either under a netting or in a glass jar, in which the blades of fresh grass and a few drops of water are placed.   The temperature of the atmosphere must be kept at about 86° F. The mid-intestine and the salivary glands must now be observed.   For this purpose, the mosquito is anæsthetised

by ether or the smoke of tobacco, and then fixed upon a piece of coloured glass by means of a needle passed through the thorax, with the back towards the glass ; then with a teasing needle we press lightly at about the thiid abdominal segment, and very gently push apart the two needles, making slight traction—the entire procedure taking place in a small drop of physiological salt solution, or in 1 to 2 per cent. of formalin. In this way the whole intestine is drawn out ; the anterior intestine is ruptured at the thoracic segment, the posterior intestines remain adherent to the last abdominal segments, which are detached from the others, and the all-important middle intestine remains free. To obtain clear preparations of the parasite in the middle intestine, it is well to detach the epithelium before fixation, examination is naturally interfered with, as these cells take on a deep stain. A homogeneous immersion lens is required for the study of the structure of the parasite in preparations that are stained ; but for its mere recognition the magnification of an ordinary dry lens will suffice. In dealing with the salivary glands, after fixing the thorax as above, we try to detach the head by slight traction with the needle, and thus sometimes succeed in extracting all the granular tubes with their excretory ducts : the anterior half of the thoracic segment must be torn off, with two fine teasing needles, if this does not occur having in this way secured fresh preparations, the *sodium chloride* or the *formalin* solution will be required for their study. If stained preparations are required, we leave the same organs adhering to the glass, and fix them with a five per cent. solution of formalin, or a saturated solution of corrosive sublimate ; then the specimen is passed through the alcohol, and stained by Bohmer's hæmotoxylin or by the ferric hæmotoxylin of Heidenheim. There is another method, from the use of which also a clear idea of the relations of the parasites to the intestine and surrounding parts can be obtained ; and it consists in fixing the whole insect in a

solution of corrosive sublimate, enclosing it in paraffin, making sections in toto, and staining the same as above described.

The entire process of development of the crescent forms in the body of the *Anopheles claviger* has been studied by Grassi, and Bignami, and Bastianelli ; and they have been able to do the same also with the *Anopheles bifurcatus* and *pictus* Ross has seen the first stage of development of the crescents in a form of *dappled-winged mosquito*, which was recognised by Grassi, in a specimen sent by Ross to Rome, as much like the *Anopheles pictus.* In Rome it is only in the *Anopheles claviger* that the complete cycle of development of the parasite has been followed ; it was seen to have the characters of a typical *sporozoön*, after the structure of the parasite had been studied in its various evolutionary phases in stained preparations. From the analogy of similar processes in other *sporozoa*, we are led to believe that in fertilised crescents nuclear modifications and processes of fecundation must take place, though we have not been able to witness them up to the present   The modifications undergone by crescents in blood taken from man, the formation of the *pseudoflagellate* odies, etc., have already been described ; and in doing so, the reasons and data for considering these forms as *gametes* were stated.   We have also observed that the natural medium, in which is completed the formation of the *microgametes* or flagella, and, as we have every reason to suppose, the fecundation occurs, is the mid-intestine of some species of mosquito.   By direct research it has, in fact, been established that in the blood contained in the mid-intestine of *Anopheles* some crescents become *flagellated*, and even individual *flagella* have been seen.   We do not obtain their regular development (nor do the crescents develop in every case) always when a patient with crescentic forms in the blood is stung by *Anopheles.*   If we examine the middle intestines of an individual of *Anopheles claviger*, kept by the *thermostat* at a

constant temperature of 86° F , a little less than two days
after it has sucked in crescent blood, we find in its walls
fusiform bodies, which in a fresh preparation appear to be
identical in form and appearance with the spindle-shaped
bodies found in human blood; they differ from them only in
being a little larger, and in having a different arrangement
of the pigment. In preparations stained with hæmotoxylin
these bodies exhibit a large nucleus, with a mass of central
chromatin, which may be round or elongated; the protoplasm
appears to be vacuolated. More rarely we see pigmented
bodies possessing the same characters, but ovoid or roundish
in shape; for the most part, the pigment is situated at the
periphery of the parasitic bodies; and it is in both spindle
and ovoid bodies found to be identical with that of the
crescent forms. The seat of the development of these bodies
is on the outside of the epithelium and basement membrane
between the muscular fibres of the intestinal walls and the
adipose tissue thereof; and it is best studied by examination
of section in toto of the mosquito. The parasites will be
found to have greatly increased in size on the third and fourth
day, and the parasitic body will be seen to have a capsule
surrounding it. It now possesses a protoplasm with a reti-
cular aspect, and the pigment is apparently in smaller
amount and irregularly disseminated. The capsule is still
more visible on the fifth and sixth days; and the parasites
themselves have enormously increased in size, up to
70 mm. or more. They project from the walls of the intes-
tines into the cœloma, and may easily be seen, even with
a low power of the microscope. In their interior may be
seen shining bodies resembling fat, which in part existed in
the previous phase; and numerous small bodies, which in
stained preparations are recognised as nuclei. Looking at
the parasite on the seventh day, it appears to contain an enor-
mous number of delicate, thread-like filaments with thinned
extremities, about 14mm. in length, arranged like rays around

one or more homogeneous masses, in which a little black
pigment is still to be seen. Exit is given to innumerable
filaments, in the centre of which will be seen one or more
granules or small bodies of nuclei chromatin in preparations
stained with hæmotoxylin or after Romanowsky's method,—
if they are crushed in such a way as to break the capsule,
the developing stages, which go on to maturation, are evi-
dently represented by the individual forms so far described,
i.e., of a *sporozoön*. This development consists essentially
in an increase in size with encapsulation ; and in successive
multiplication of the nucleus, up to the formation of very
small nuclei, around each of which is gathered a little pro-
toplasm, the *sporoblast* without capsule. The *sporoblasts*
are transformed into the *filiform* elements described—the
sporozoites ; so that the mature *sporozoön* on the seventh day is
composed of the residue of segmentation and a thin capsule
with innumerable *sporozoites*. The torn and flaccid capsular
membrane in the succeeding days is found to be adhering to
the intestines, and near to it the *sporozoites*, which later
accumulate in great number in the tubules of the salivary
gland, or within the cells of this gland, or in the
glandular lumen. It has been repeatedly demonstrated by
experiment that at this point the *Anopheles*, biting a
healthy man, inoculate him with the *sporozoites* along
with the saliva, thus determining an æstivo-autumnal
fever, after a period of incubation, the temperature
appears to have a certain influence upon the time required
for the completion of the life-cycle in the *Anopheles claviger*.
The development does not seem to occur at all at a tempera-
ture of from 57° to 59° F., and at from 66° to 71° 6′ F. it is
much slower than that which has been described. It must
also be noted that we may find, in addition to the forms
described, in the mid-intestine, within the capsule, peculiar
brown bodies, varying in size and irregular in shape, some
like rods, others ovoid or round, some straight and others

curved. The retrogressive changes in the *sporozoa* are supposed to give rise to these bodies ; and this because of their irregularity and sometimes stratified appearance   They, like the bodies seen by Ross in studying the *proteosoma* coccidia, may be found within broken or shrunken capsule, or else within a large capsule, which is apparently distended by its contents.

Grassi, and Bignami, and Bastianelli have sudied the development, in the *Anopheles claviger* and *bifurcatus*, of large pigmented bodies of the *tertian* parasites ; and the two last-mentioned observers have traced the entire life-cycle of the parasite in question in the latter insect. The formation of the *macro* and the *microgametes* has been described already, as also their structures ; and we have seen that the ulterior life-phases of these bodies are normally developed in the mid-intestine of the anopheles. Here occurs the fertilisation of the *macrogametes* by a flagellum or micro-gamete ; and the fecundated body then penetrates into the intestinal wall where it continues its development. As before mentioned, the theory that the *sporozoön* developed in the anopheles is the fecundated *macrogamete* is founded upon analogy ; for, up to the present time, no one appears to have had the opportunity of actually witnessing the process of fecundation, nor of following the first succeeding nuclear changes. We can easily see a certain number of tertian bodies in the thickness of the walls of the middle intestines, specially in its terminal portion, in the case of anopheles which have bitten a tertian patient having in his blood the forms regarded as gametes, and which are kept, for about 40 hours after the puncture, in a constant tem-perature of about 86° F. They appear as round, pigmented bodies, very transparent, and with distinct outlines, and contents varying in appearance, sometimes uniform, some-time vacuolated, or else divided into masses. They are easily recognised by the characteristics of the pigment, which are

those typical of the tertian pigment, which is usually immo-
tile, and only exceptionally in motion.   In preparations
stained with hæmotoxylin, we see that the protoplasm has
a reticular appearance, and that the chromatin has increased
in amount, relatively to the amounts seen in the same
bodies before they have penetrated the intestinal wall, and
not rarely it is undergoing division or had divided into
various little masses.   The diameter is one and a half to
two times that of a red blood corpuscle at this stage of
development.   The parasites are seen to be from one-fourth
to one-third larger on the third day than on the second.
They possess a very evident cystic wall; and in fresh
preparations their contents are seen usually to be divided
into little masses, between which is the pigment varying in
number from 8 to 15 of round, ovoid, and deeply-coloured
nuclei are to be found in stained preparations.   The cyst wall
is very distinct, and the size of the cystic body has increased
about one-fourth on the 14th day.   The protoplasm pre-
serves a reticular, almost spongy, appearance; and the
nuclei are more numerous—20 to 30—and somewhat smaller
than in the preceding stage.   The parasites, which from
the beginning have been situated outside of the intestinal
mucous membrane, between the fibres of its walls, between
the fourth and fifth days begin to project between the fat
cells into the cœloma.   They continue to increase in size,
so that they are easily visible with a low power of the
microscope.   In fresh preparation they look like the bodies
of the preceding stage and in stained preparations the
nuclear division is seen to continue, so that more numerous
and smaller nuclei are formed.   Filaments or *sporozoiles*,
arranged side by side and in groups around masses of an
apparently amorphous substance, are, as a rule, seen within
the capsule on the third day.   The presence of amorphous
masses, which are usually multiple and which represent the
residua of segmentation, are seen in stained preparations ;

but at this time some capsules in fresh preparations appear
to be almost filled with *sporozoites*. Our description of the
mature *sporozoa* of crescent origin applies to the structure of
the *sporozoites*. It must be remembered, that the description
in question is somewhat schematic as regards the size of the
body and the stage of development in the several days after
the puncture We may, in fact, observe cystic bodies, abou
as large as those of the fourth day, already mature, that is
to say, completely filled with fully developed *sporozoites*.
Furthermore, cystic bodies, of various size and in different
stages of development, are often seen in mosquitoes which
have bitten a patient only once From this it follows, then,
that the development of the malarial parasite does not occur
with the same regularity as to time in the intestine of the
anopheles as it does in the blood of the human subject.
The brown bodies described by Ross in the so-called *pro-
teosoma coccidia*, and found in Rome in the crescent *sporozoites*,
have not been found in mosquitoes nourished with tertian
blood. The broken and shrunken corpuscles, after about the
17th day, have been found in the intestines and the *sporozoites*
in the cells or the excretory ducts of the salivary glands.
The *sporozoites* are either of the form they are in the capsule
in the intestine, or else short and thick in the latter.

Bignami and Bastianelli affirm that the following are the
differences between the crescent and the tertian sporozoa in
the Anophelic life-cycle, which, though slight, admit of a
differential diagnosis in some stages of development at least
Firstly, in the tertian sporozoön the sporozoites are less dense
and more regularly arranged, sometimes in rays around the
residua of segmentation, than in the capsule of crescent
origin. Though there are mature corpuscles which exhibit
no appreciable differences, the residua of segmentation in the
case of the tertian parasites are usually composed of severa
granular blocks, which are more numerous than in the case of
crescent parasites. Secondly, in the crescent the form of the

sporozoön in the first stages of development is either spindle or ovoid,—in the rare cases in which it is oval, this may possibly be due to the stretching during the extraction from the intestines, while in the tertian it is round, or, as just parenthetically expressed, oval. Thirdly, at the same stage of development the crescent sporozoon has a more distinct outline and greater refractive power; so that, while the tertian is more transparent and in the first stages is visible only by a homogeneous high power immersion lens, it is well seen even under a low power. Fourthly, the quality of the pigment is naturally identical with that of the corresponding parasites in the human being. Fifthly and finally, the nuclei of the tertian *sporozoön* are less numerous and larger than those of the crescent *sporozoön* at the same stage of development, *i.e.*, after successive divisions.

Numerous experiments have from time to time been conducted as to the development of the quartan parasite in *Anopheles claviger*, but seldom with a positive result. In one Anopheles claviger nourished upon a woman who had suffered for eighteen months from quartan fever, and who had many *parasites* in the blood with a few rare *gametes*, there were found two corpuscles containing the characteristic pigment of the quartan parasite. These capsules, when three days old, had about the same dimensions as the two days' capsule of crescent origin. The negative results obtained in so many researches are probably due to the extreme rarity with which flagellated bodies are found in quartan blood. It is possible that in this species of infection, in which the parasites have grown so flourishingly in human blood, there may be so complete an adaptation of the parasite to this mode of existence, that after a while it may entirely lose the power of producing bodies capable of ulterior development in a different atmosphere. It appears from the most recent researches made by Bignami and Bastianelli, who have succeeded in observing the whole life-cycle of the

quartan parasite in *Anopheles claviger* that positive results are obtained only in cases which have lasted a very long time; that only in cases which have had several relapses do the *gametes* make their appearance; and that the results are negative when recent cases are employed for experiment.

Many authors have affirmed that it is possible that there may be other life-cycles; and that the forms described above for the crescent and the tertian parasites represent only the life-cycle of these beings. In addition to the forms already mentioned, some writers have noted, in relation to the development of the crescents in *Anopheles claviger*, tubular or *ampulla-like* masses of small, round or oval bodies, some hyaline, others covered with a dark-yellowish brown membrane; in the same preparations, indeed, we may see the various phases of development of thick membrane which surrounds the hyaline body. These bodies, which are found within the intestines or in the dorsal vessel, appear to be resistant spores; and, as they greatly resemble the brown bodies of unknown significance, which are found within the capsule of malarial *sporozoa*, the authors whom we have quoted, at the beginning of their researches held that they were identical with these brown bodies, and considered them to be a resistant form of the malarial parasite in the mosquito—a form capable of passing into water at the insect's death, and then going through a new life-cycle. Later researches have demonstrated that the development of the brown spores, from the typical forms of malarial *sporozoa*, cannot be followed; they then held that these were special parasites, probably another parasitic *sporozoön* of the *Anopheles* having no relation to the malarial parasite. No known form of the malarial *sporozoa* of the mosquito, possessed of the significance of a resistant spore, has therefore as yet been observed. The hypothesis that the malarial parasites, through the *eggs* and *larvæ*, pass from the infected mosquito to its progeny has derived the semblance of probability from what is known of the

biology of the parasites in *Texas fever*; and an attempt has
been made to solve the question in regard to the parasites of
human malaria by two methods of research.   On the one hand,
the eggs and larvæ of supposedly infected *anopheles* were
studied; and, on the other hand, men were caused to be
bitten by mosquitoes born in the laboratory, and which were
therefore known not to have been nourished by malarial
blood to ascertain whether they bore in themselves germs of
infection from their birth being the object of such experi-
mentation   The former class of researches resulted in the
fact that in the well-developed eggs of the *anopheles* there
were not infrequently found cystic bodies containing eight
easily-coloured little bodies, which may be considered as the
spores of a *sporozoön* with eight *sporozoites*.   But it has not
been possible to determine whether there is any relation
between these bodies and the malarial parasites : in fact, it
would seem that there is none.   On the other hand, no forms
at all like the malarial parasite have been found in new-born
mosquitoes ; neither has it been possible to follow the develop-
ment of these bodies in the larvæ.   Entirely negative results
have also been given by the second class of experiments.   Of
the numerous healthy persons who allowed themselves to be
bitten in the laboratory not one took the fever.   The sub-
ject is still being investigated in various quarters.   The only
deduction that we can make so far is that the *malarial para-
sites pass from the sick person into certain species of mos-
quitoes, and from these, after having pursued the life-cycle
described, they return again to man.*

CHAPTER XI.

MORPHOLOGY OF MOSQUITO.*

The word "mosquito" is the Spanish diminutive of "mosca," a fly, and the name is correctly applied, since mosquitoes belong to the order of two-winged insects, or true flies, Diptera. They constitute the family Culicidæ, of which some four hundred and fifty species are known at the present time.

Distribution.—Since the discovery of the agency of mosquitoes in the spreading of malaria, they have received a great deal of attention, and new species are constantly being found. The majority are tropical, but their range of distribution is nearly universal, extending from the Equator northward and southward, over the temperate zones into the Arctic and Antarctic regions.

Though mosquitoes inhabit generally in low and swampy districts, they are also recorded from high altitudes, and Stephens and Christopher in a Report to the Malaria Commission of the Royal Society, state that they are troublesome in the Himalayas at a height of 13,000 feet. A well known malarial species is recorded by them at 5,000 feet. In India mosquitoes are numerous in the low-lying regions of the south and on the plains and Terai, but also in many places in the rocky mountains and jungles.

Habits —As a rule, mosquitoes are frail insects and weak flyers. In rain and winds they do not have hiding-places. The malarial mosquito (Anopheles) avoids places where draughts exist, and seldom flies more than a few hundred yards. (An Indian species of the genus flies a quarter of a mile, but rarely as far as half a mile.) The malarial mosquito, as a rule, spends its entire life in the immediate neighbourhood of human dwellings.

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* The Malaria Mosquito, (a guide leaflet), American Museum of Natural History, by B. E. Dohlgrin (Extracted.)

Mosquitos are most active at early dawn and after sunset. They seem in general to avoid strong light and to prefer dark colours. The hours of daylight are spent by most species hiding in some secluded spot in a tuft of grass or a bush or shady damp woods, trees and swamp, while the malaria mosquito finds some dark corner indoors, where it passes the day. Anopheles do not make a humming sound, so that very frequently people are not aware of having been bitten by them.

Hibernation.—In the autumn all the males die ; while the fecundated females seek winter quarters. The malarial mosquito, which is essentially a house mosquito, may be found hibernating in dark corners in cellars, sheds or attics. The strictly out-of-door species finds winter quarters in the woods or in the fields. Large numbers of the insects undoubtedly perish during severe winters, but, under ordinary conditions, mature females survive to furnish locally the first brood of the following season. A warm day in early spring brings the insects out of their dullness. In tropical countries the period of activity for the mosquitoes is the hot season which is too well known to the resident of Indian climate.

Food.—The food of mosquitoes consists ordinarily of the nectar and juices of plants and fruits. This is always true of the males, whose mouth-parts are not at all adopted for stinging. In certain species neither sex seems to have any taste for blood ; while, on the contrary, it is well known that mosquitoes living far in the woods, in the swamps, or in the Arctics where their chances of obtaining a meal of blood may be almost *nil*.

It has been thought that a full meal of human blood is necessary for the female " malaria mosquito," in order that she may lay her eggs, but this is certainly questionable. Mosquitoes by no means confine themselves to human, or even mammalian blood ; they suck with eagerness the blood of birds

and reptiles whose skin they may be able to pierce. They have frequently been observed feeding upon other insects. They require water, but may exist for months without any food whatever.

Length of life.—The average length of life of female mosquitoes is not less than a month or two, but hibernating females must live at least six or even eight months. The life of the males is much shorter, and may not exceed a few days in duration. To compensate for the shortness of the life of the males, they greatly outnumber the females. Since a recently hatched mosquito becomes full-grown in two or three days, and it may lay its first batch of eggs within a week, there may be as many as a dozen or more generations in the course of a year, in favourable localities, but seasonal conditions necessarily exert a great influence on the number of brood. In dry climates breeding is infinitely small, as a rule, breeding is confined to the end of the rainy season, in tropical countries it may extend throughout the greater part of the year.

Breeding place. The female mosquito lays its eggs, from 50 to 200 in number, on the surface of any convenient quiet body of water.

Though mosquitoes of the various species may differ widely in many minor details, such as *size, colour, form of scales* and *markings on the body, wings* and *legs*, in all essential respects of structure and life-history they are just the same.

THE MALARIA MOSQUITO.

Anopheles' Eggs.—Mosquito eggs are minute bodies, and are generally ovoid in form, but the particular configuration of their covering, of chitin varies considerably in different species. The egg of Anopheles is boat-shaped, with one end somewhat pointed, the other rounded. The lower surface, the bottom of the boat, is strongly

convex and reticulated, the upper surface, the deck,
is more flattened.   The egg is provided on the sides with
corrugated air-chambers which serve as floats.   When
recently laid the eggs appear almost white in colour, but
they darken rapidly, and in a few hours becoming nearly
black.

Arrangement of Eggs.—In the process of deposition
the eggs of the common mosquito unite to form raft-like
masses, which are known as "egg-boats."   The eggs of
Anopheles, however, are deposited separately, but they may
be found arranged in various patterns on the surface of
the water, forming star-shaped groups or adhering side
by side to make miniature "pontoon-bridges."   The eggs of
certain species are never laid on water, but on mud, perhaps
at the edges of pools, and are said not to develop at all,
unless they be left dry for at least twenty-four hours.

Hatching.—When the eggs are ready to hatch, in
about two or four days after they are laid, a small cap-like
portion of the envelope bursts off at the rounded end of the
egg and the larva escapes.   In the "egg-boats" of Culex the
rounded end of each egg is directed downward and the larvæ
escape into the water from the lower surface of the float.

THE LARVA.

Mosquito larvæ are popularly known as "wigglers"
or "wrigglers."   At the time of hatching, the larvæ of
the malaria mosquito are minute, brownish and round
headed.   As soon as freed from the egg the larva begins
to feed.   It grows rapidly, and, if the food-supply is abund-
ant and the temperature of the water is not too low. it
attains its full size in a few days.   The body is divided into
the *head*, the *thorax* and the *cylindrical abdomen* of nine rings.
In a newly-hatched larva the latter regions can hardly
be distinguished from each other, but as the larva grows the
three fused rings of which the thorax consists become

enlarged and flattened. Legs are absent, but both thorax and abdomen bear a great number of symmetrically placed pairs of branched feather-like hairs, arranged in a manner characteristic of the species. These hairs project laterally and aid in maintaining equilibrium, but undoubtedly they serve other purposes too, being also organs of touch and possibly of respiration On the back of the abdomen are five or six pairs of dark-brown palmate structures, which float on the surface of the water, when the larva is at rest, and aid in maintaining the *horizontal* position of the body which is characteristic of larvæ of the genus Anopheles.

The next to the last ring bears on its upper side the short "siphon," which reaches the surface of the water, when the larva floats in its usual position. In the siphon are the openings of the respiratory tubes. The larva is strictly air-breathing and does not normally remain away from the surface of the water, except when disturbed, and then only for a short time.

Effect of oil.—The oil, acting mechanically, closes the openings in the respiratory siphon and causes the larvæ to die from suffocation. Its destruction can be effected by means of film of oil spread on the surface of the water.

The last ring of the abdomen has terminally two pairs of bristles and four elongated sac-like appendages with very thin walls, the "blood-gills." On its under side it bears a large fan-like arrangement of branched hairs which seems to serve as a keel or rudder.

Head of Larva.—The head of the mature larva is large and rounded, and is brown in color. It is united to the thorax by a membranous neck which allows considerable freedom of movement. Its upper surface is characteristically marked by dark-brown spots and bears rows of branched hairs. On the sides of the head are the *antennæ*, extending forward, and behind these are the eyes. In front, on the under side is the mouth, which is surrounded by a formidable

armature, and overhanging the mouth-parts and at the most anterior part of the head are two moustache-like brushes. Below these and behind them are two *mandibles* which move laterally and bear strong spine-like teeth for crushing food. On either side of the mandibles project the cylindrical maxillary palps, and below the mandibles are the flattened maxillæ beset with fine hairs. Below all of these mouth-parts is the so-called small triangular " lower lip." Anopheles' larvæ exhibit a curious habit of suddenly twisting the head. The larva feeds with its head turned so that the lower side, which bears the mouth, is directed upward.

Food of Larva.—The food of the larva consists of the microscopic animals and plants which abound at the surface of the water.

The malaria mosquito larva may be readily distinguished from the larva of the Culex mosquito by the shortness of its siphon and its horizontal position in the water. The common " wrigglers " have elongated siphons and are always found hanging obliquely, or even vertically, head downward, the tip of the siphon only reaching the surface.

Hibernation.—The larvæ are most likely to be found in small and undisturbed bodies of water, such as accumulate in little hollows between tufts of grass, in meadows, or in ditches where there is no perceptible flow. Where there is any current in the water the larvæ are easily swept away, and those that occur in moving water are always found along the edges of the stream, where they are out of reach of the current. Such places as neglected *tin cans* or *broken bottles, rain barrels, cisterns*, ponds, collection of water, and deep wells, may be swarmed with larvæ.

Duration of Larval stage.—The duration of the larval stage is usually from seven to fifteen days. During this time the various parts of the adult insect are in process of development under the larval skin. In older larvæ the adult

eye, for instance, may be seen as a crescentic dark mass lying near the larval eye. The legs and wings of the future "fly" may be seen forming within the larval thorax. In due time, when this proceeded far enough, a T-shaped split occurs in the back of the larval skin and through this the insect emerges as a *pupa*.

THE PUPA.

Habits of Pupa.—The pupa which escapes from the larval skin forms the next stage in the development of the insect. It is aquatic in habit and ordinarily leads a brief and comparatively quiet life. It does not feed. When at rest, it floats at the surface of the water, breathing through a pair of funnel-like tubes. Under the transparent integument of the pupa may be seen the outline of the body and the appendages of the developing mosquito.

Duration of Pupal life.—The duration of the pupal stage is usually from two to five days, but it may, under favourable conditions of temperature, be prolonged to weeks. On the other hand, the threatening danger of draught or the presence of disagreeable substance in the water, such as the kerosine-oil, used for destroying mosquitoes, may very much hasten the exigency of the insect.

Formation of the adult—The pupa represents that period in the metamorphosis of the insect during which the internal changes begun in the larva, which are to result in the formation of the adult mosquito, are continued and completed. Under the pupa skin a new integument is secreted which becomes the final external covering of the fly. Its appendages, hairs and scales may be seen fully developed in later pupal stages.

When the formation of the mosquito fly is complete, the pupa skin bursts along the middle of the back and the adult extricates itself from the floating case. At this period, large

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numbers of mosquitoes perish, because, until their legs and wings are thoroughly hardened, a slight gust of wind or a small ripple of water will upset and drown them. This makes it possible to bring about the artificial destruction of a large proportion of the insects, through the simple introduction of tidewater into mosquito-ridden marshes.

THE ADULT MOSQUITO.

Body-covering.-- The body of the mosquito, like that of all other insects, is covered with a dense, though very thin, continuous layer of a hard substance, "chitin," secreted by the true cellular skin, or hypodermis, which lies underneath it. The chitin not only affords protection to the body, but also gives support to the limbs and wing-veins and forms in fact an external skeleton, on the inner side of which the muscles of the insect are attached. Wherever rigidity is required the chitinous coat is thickened, but elsewhere it remains thin to permit movement of the body segments.

Divisions of body.—Three main regions of the body may be easily distinguished, the small rounded *head* with its appendages, the relatively large *thorax*, and the elongated *abdomen*. The head, which is connected with the body by means of a rather slender neck, bears the mouth-parts and special sense-organs. The thorax, which consists of three closely consolidated segments, bears the organs of locomotion, the legs, one on each segment, the wings on the middle segment and a pair of minute balancers on the third. The abdomen is distinctly segmented and consists of eight rings, but, except on the terminal segment, it bears no appendages. The spherical head is somewhat flattened in front.

Head.—The anterior portion of the head is occupied by two large compound eyes ; in front of the eyes are the antennæ.

Anennæ.—The antennæ are organs of hearing, and by means of them the male is able to detect the presence of the female.

Proboscis.—Below the antennæ, at the very front of the head, are the mouth-parts, constituting the so-called " proboscis " This consists of several members. The principal one, lying above all the other mouth-parts, is the " labrum." Under the labrum there is a delicate chitinous lamella, the hypopharynx. The hypopharynx is closely applied to the labrum along its entire extent, and by closing the groove therein from below, forms therewith the tube through which the mosquito sucks up blood or other liquid food. A fine tubular channel which runs along the medium line of the hypopharynx serves to conduct the poison that the mosquito pours into the wound when sucking blood. Along the sides and below the tube, composed of these two mouth-parts, there are two pairs of very slender chitinous rods, expanded at the ends into lancet-like blades set with fine teeth. One pair, the " mandibles," are exceedingly delicate ; the other, the " maxillæ," are stouter and have larger teeth.

All these mouth-parts, *viz.*, the *labrum*, the *hypopharynx*, the *mandibles* and the *maxillæ*, form a very compact bundle, which, when not in action, is almost entirely contained in a groove on the upper surface of the lower lip or " labium." Its outer surface is beset with scales. Of the whole bundle of mouth-parts only the labium and upper surface of the labrum are ordinarily visible.

The female alone sucks blood. In the male the maxillæ are lacking, and the tip of the labrum is blunt and unfit for piercing.

The Palps.—On either side of the proboscis there are two long pointed appendages of the maxillæ, the maxillary *palps*, which serve as organs of touch. In the female Malaria Mosquito they are slender and of uniform thickness ; in the male the terminal segment is enlarged and bears long hairs. In both sexes of the Malaria Mosquito the palps are long, equal in length to the proboscis, and covered with fine scales. In the common Culex Mosquito, the palps of the female are

short, not more than half the length of the proboscis ; those of the male are long, but their terminal segment is not enlarged though set with long hairs. This furnishes a ready means of distinguishing the Malaria Mosquito from the Culex.

The slender neck connects the head with the second division of the body, the thorax. This is greatly enlarged to accommodate the strong wing-muscles which it contains. The segment, which bears the wings, exceeds the other in size and forms the entire dorsal portion of the thorax.

Wings.—The delicate membranous wings are strengthened by ribs or veins, closely beset with scales. The arrangement of scales varies in the different species of mosquitoes. The Malaria Mosquito is distinguished by the presence of *four dark spots* in certain characteristic positions on its *wings*, and hence its specific name " maculipennis," or " spotted-winged." The margin of the wing bears several rows of scales, long and slender scales alternating regularly with rows of shorter ones, producing a beautiful fringe.

Legs.—Each of the segments of the thorax bears a pair of legs. The legs are connected to the body by the " coxæ," or hip-joints, which are constructed so as to permit great freedom of movement. Each leg consists of seven pieces. The first is called the *femur*, the second is the *tibia*, then follow the *tarsal* joints, five in number, the last of which bears a pair of *claws*. In the male one of the claws of each foreleg is greatly enlarged. When the mosquito walks or rests, it supports itself on several of the tarsal joints, and in flight they help to balance the body and determine its inclination. They are often carried raised and curved forward over the body, especially when the mosquito is stinging.

Abdomen.—The abdomen is closely united to the thorax. Its eight rings, or segments, are each composed of an upper and a lower shield of chitin and a soft connecting

membrane. The abdomen tapers gradually towards the tip, and the last segment in the female mosquito bears the ovipositor by means of which the eggs are laid, and with the aid of the hind legs, arranged on the surface of the water. In the male, the last abdominal segment terminates in a pair of claspers.

Colour of Adult —The colour of the mosquito can be said in general to range from light-yellow to dark-brown and almost black. Some species are nearly colourless, or of a very transparent light-green. The malaria mosquito is brown, described as above, the colour increasing at first with age till the chitin becomes thickened. The thorax is dark-brown above, with a light stripe in the middle and one on each side of the back. The upper shields of the abdomen are dark-brown, the lower ones lighter and more yellowish. The legs are dark-brown above, sometimes with a purplish tinge, and are lighter below, with distinctly yellow spots at the knee-joints. The proboscis and palps appear very dark-brown or purplish-black. The back of the thorax and the entire abdomen are covered with long, golden hairs.

THE INTERNAL ORGANS.

Two pumps.—When the mosquito bites, blood is pumped up into the "sucking-tube" by two pumps. The first and smaller pump lies just above the junction of the labrum with the head and forms a direct continuation with the tube. The second larger and more efficient pump lies further back in the head and is dilated by powerful muscles. This is in great part in the neck of the insect and gives off, just beyond its entrance into the thorax, three food-reservoirs, two small ones above, and a third, elongated sac below, which reaches far into the abdomen.

Food-reservoir.—It is the blood stored up in the reservoir, which in its greatly distended state may be seen through the thin pleural membrane, that gives to the mosquito

the red colour noticeable after a full meal. The stomach is a continuation of the œsophagus and is tubular, narrow in front, but dilated into a sac behind. At its posterior end is a valve-like constriction just beyond which there open into the intestine five excretory tubules. After one or two rather sharp curves, the intestine is continued to the terminal end of the body.

Respiration.—Respiration is carried on by means of a system of air-tubes, or tracheæ, which open to the exterior by two main openings on either side of the thorax, and by eight smaller ones in the soft membrane of the abdomen.

Circulation.—The circulation of the blood of the insect is maintained by the heart, which is a tubular organ lying directly under the upper chitin shields of the abdomen. It is continued forward in the thorax as a vessel, the " aorta," through which the blood is pumped to the head. Into the blood within the body cavity of the mosquito, the malarial spores grow in its stomach wall and eventually they escape. Through the circulation of the blood the spores then find their way into the salivary or poison glands.

Poison glands.—These important little glands, which supply the irritating poison of the mosquito bite, lie within the anterior part of the thorax just beyond the neck. The secretion from each three-lobed gland is conducted forward into the head by a fine tube, the salivary duct. In the head the two ducts join and the common duct empties into the salivary pump. This, in connection with its continuation, the salivary channel in the hypopharynx, forms a practical syringe by which the poisonous saliva is automatically forced out at the point of the proboscis during the act of feeding. It has been thought that the saliva serves to prevent the clotting of the blood in the mosquito's sucking tube. Its irritating effect is, however, well known, and it is, furthermore, with this salivary secretion that the malarial spores are injected into the human circulation.

CHAPTER XII.

MALARIAL ENVIRONMENT.

Malaria has in some localities prevailed for hundreds of years, though in others there have been *endemics* and *epidemic* observed. Such predispositions Celli terms the " *localistic predisposing causes.*"

DISTRIBUTION OF MALARIA.

The disease occurs in almost all parts of the world ; and there are few diseases which have so wide a distribution. As stated, there are certain principal foci where the disease is permanently endemic. These regions are chiefly in the warmer temperate and tropical countries. Generally speaking, the farther one departs from the Equator, the less common are the malarial fevers. A sharp line of delimitation cannot be drawn Occasionally cases have, according to Celli, been observed as far north as Irkutsk in Siberia, Hapanandra in the Gulf of Bothnia (65° N. lattitude), Juliushaab, Southern Greenland, and new Archangel in Alaska, while towards the south malaria has been reported to exist as far as the isotherm of 60°. It must be remembered, in considering any statistics concerning the distribution of malaria, that the diagnosis of malarial fever has been, till comparatively recent, and is, unfortunately, far too frequent to-day, made upon a very insignificant basis. In many regions at the present time an intermittent fever with chills is without further investigation assumed to be of malarial origin ; and even at the present time, in some of the large cities and towns abroad, there are statistics which are absolutely incorrect, showing thousands of deaths from the disease every year. All are agreed that the principal haunts of malaria are the tropical countries. In Europe the disease is common

in the low lands about the coasts of Italy, Sicily, Corsica, Greece, the Black and Caspian Seas, and the Volga. About the coasts of certain parts of France, Spain, and in Denmark and Sweden, an occasional case is seen. In Holland and Belgium the milder forms of the disease are not uncommon ; while a few cases of the same nature are seen in Germany about the north of the Elbe, and along the Baltic coast of Prussia, in Silesia, the plain of the river Mark, and in Pomerania. In tropical Africa the disease appears in its most severe forms, specially along the west coast. The chief foci of the disease in Europe are Italy and Southern Russia. In India, Ceylon, and the East Indies, it is particularly common ; in India the disease is endemic all over the country, but the chief foci are in low lands and the Terai, where it is very malignant, while in Southern and South-Western China it is also endemic. In Japan the disease is rare. In the Western Hemisphere malaria is seen in the low lands about the coasts from New England to Florida, though above Virginia the severe forms are rare. In the Gulf States and along the banks of the Mississippi and its tributaries, in most of the Southern States, the disease is almost always present. About some of the great lakes, both in the United States and in Canada, malarial fevers are occasionally seen ; while from the Pacific coast a certain number of cases are from time to time reported. Some of the most fatal cases of the disease are to be encountered in Central Africa, Mexico, and Cuba. The dreaded Chagres fever of the Isthmus of Panama is a pernicious malarial infection. About the low lands of the eastern coast of South America, particularly in the Guianas and in Brazil, the disease is *endemic* in its most malignant forms. On the west coast it is less frequent, though its occurrence in Peru and Bolivia has been known for years. Indeed, it is from the Peruvian Indians that we learnt the value of the specific remedy for the disease. In Australia, new Caledonia,

and the islands of the Pacific the disease is very rare ; and, notwithstanding the existence of extensive low marshy tracts, it is quite unknown in some regions, such as Hawaii, Samoa, New Zealand, and Van Diemen's Land. The infection may often be traced to a previous sojourn in a malarious district in cases of malarial fevers which occur sporadically in regions where the disease is uncommon. Extensive epidemics and pandemics of malarial fevers, spreading over the greater part of the world, have been described. The true nature of the affection, in most of these instances, admits of considerable uncertainty.

PHYSICAL GEOGRAPHY.

The prevalence of malarial fever is rather considerably influenced by the physical geography of the country. According to Laveran, the " principal *foyers* of *paludism* are situated on the coast or along the banks of large rivers." High altitudes are usually free from malarial fevers, and mountains and plateaux in the neighbourhood of malarial districts are often used by the inhabitants as *sanitaria*. The high altitudes may not be a protection, as fevers occur in the Tuscan Apennines at a height of 1,100 feet, in the Pyrenees at 5,000 feet, on the island of Ceylon at 6,500 feet, and in Perus at from 10,000 to 11,000 feet, on the Himalayan ranges at 12,000 feet. It is, however, by no means improbable that many of these fevers which have been called " Malarial, "—as in the case of the " mountain fevers " of the Western Estates, which is for the most part, probably, enteric fever—are in reality of some other nature.

THE SOIL.

For a great many years Malaria was held to be of *telluric* origin, and that the pathogenic germs rose into the air from the soil and from stagnant pools of water ; and tnis belief gave origin to the study of the soil in malarious

regions, a study which was prosecuted in all directions. The endeavour was made to discover in what way the malarial germs were carried a certain distance above the ground, specially at certain hours ; the geological nature of the soil in places where malaria exists was determined, and a search was made in the ground for the malarial parasite. As *argillaceous*, *calcareous*, and even *granite* soils may be found in malarious localities, the geology of an infected district is not of any importance. It is not the nature of the soil that exerts an influence in the production of malaria, but the fact that beneath a more or less thick stratum of *humus* there is an impervious layer ; for example, calcareous *tufa*, *marl*, or clay ; the consequence of this is that the soil is permanently moist, and there is a layer of water at the bottom of the permeable layer, while there are pools formed in the depressions of the surface. In the Roman Campagna, for example, such conditions exist. To demonstrate the import-ance of this factor, we may recall the example given by Meunier of what took place when the necessary evacuations were made for the railway from Madrid to the Escurial. For a distance of 50 kilometres from Madrid no cases of fever occurred among the labourers, but in the constructions of the second half of the line, the workmen suffered severely from malaria. There was no difference whatever in the hygienic conditions, but there was a difference in the nature of the soil, which was for the first half diluvial and sandy, but for the second half of the distance *granitic* and *schistous*. The fact that malarial endemic exists by preference in *low, marshy* places, in the *deltas* of large rivers, in the broad alluvial plains bordering wide rivers, and in valleys in which are swamps and water-courses, may be taken as proof that mala-rial fever is related to the humidity of the soil and to the presence in it of collections of water. The presence of marshes was held to be of great importance by the physician of former times ; and Lancisi recognised as the only cause of

intermittent fevers the noxious effluvia rising from swamps. He made a distinction between noxious marshes and those of a harmless character. The noxious swamps were those of the wide extent and shallow, in which, although there might here and there be an intermittent current, for the great part of their circumference, specially when the banks were flat and covered with rank vegetation, the water was stagnant ; it was from the death and decomposition of the myriads of insects and of the marshy vegetations that the noxious effluvia arose. The harmless bogs were those in which the water, either fresh or salt, was for the most part deep, in constant motion, containing little slime, with many fish, and specially if the banks were high and not grown over with canes and weeds. Lancisi says that he has seen mala-rial endemics disappear after the drying of bogs. He records an instance in point. As a sequence of the formation of a marsh, in Rome in the Celimontana valley, near the church of San Giovanni in Laterano, there occurred an endemic of fever and a plague of mosquitoes, and in the neighbouring hospital of San Giovanni there were several cases of perni-cious fever that summer ; but when the marsh was filled up, by his orders, the endemic ceased in a short time. As there are marshy places where malaria does not exist, and mala-rious districts, which are not swampy, it is not correct to assume that the presence of marshes and the occurrence of malaria are too closely connected facts, although swamps are not infrequently found in malarious places. If, as Tommasi Crudeli observes, the malaria in the Roman Cam-pagna were dependent upon the presence of swamps, it would prevail over a very limited area. But the same author remarks, that, in the malarious districts where no swamps exist, there are to be found many collections of water, little ponds and pools all about, fed by the rains or by the subsoil water. These collections of waters are more than sufficient for the development of mosquitoes, specially the malarial varieties,

which require pools surrounded with vegetation for their sup-
port.   The prevalence of malaria may be favoured in addition
to these swamps, stagnant pools, etc., by the presence of rice-
fields, the places where hemp is macerated, and the ponds on
the sea-shore where the salt-water is mixed with the fresh.
Even the irrigation of cultivated fields may be a cause of
malaria ; and the history of irrigation in Southern Cali-
fornia has made it plain that if irrigation works are not to
become producers of malaria, drainage must proceed *pari
passu* with the irrigation ; malaria is very prevalent when
this is not done.   Indeed, efficient drainage of marshy dis-
tricts which have been rich in malarial fevers has a marked
effect upon the frequency and severity of the manifestations
of the disease.   Years ago, malaria was common in the sur-
roundings of London, which were marshy and ill-drained ;
to-day, thanks to good drainage, the disease is unknown there.
The effect of good drainage upon the Roman Cam-
pagna has been very striking, the severity of malarial fever
diminishing rapidly.   The low lands of Holland used to
be the seat of very severe malaria ; to-day, only occasional
cases of the mildest forms of the disease occur.   A malaria
endemic may be produced by anything which results in the
formation of pools of stagnant water, such as inundations,
the denudation of hills, ploughing, and, in general, any
upturning of the soil in the construction of railroads, canals,
fortifications, etc.   Inundations have sometimes been followed
by a recrudescence of malaria in places where the disease
had formerly existed.   Frerichs, in 1854, observed an endemic
of grave and even pernicious fever, following an overflow of
the river Oder in Silesia, where previously only mild cases
of malaria had existed.   Although it is true that the felling
of timber in the plains may contribute to the sanitation of
such places, the same thing in uplands may, in consequence
of hydraulic disturbances thereby produced, be a cause of
aggravation of malarial endemics.   According to Pellarin,

who is cited by Rho, in the island of Mauritius, where, after
the denudation of the hills, the little mountain torrents which
formerly ran down to the sea, now disappeared on the way
and ended in pools of stagnant water, while in the rainy
season they often overflowed the same country, forming tem-
porary marshes. Coincident with these telluric changes
the malaria on the island became more widely spread and
graver, and cases of pernicious infection occurred. Some
years ago, an endemic of malaria occurred in the Trastevre
quarter of Rome when the works preliminary to the banking
of the Tiber were begun. Even the works undertaken for
sanitary and economic purposes may be the cause of an out-
break of malaria, or of an aggravation of the already existing
endemic. There are many cases on record in which the
denudations of a soil covered with forests or rank vegetation,
or the turning up of the soil in a district which was previously
free from the disease, may be followed by an outbreak
of malarial fevers ; while in other regions where the disease
already exists, similar interference with the vegetation
or the soil may greatly intensify the severity of the
process. An example of this latter condition is shown in
the severe outbreak of malarial fever which was associated
with the excavation of the Panama Canal. In Paris,
which for many years had been free from paludism, the
digging of the canal Saint Martin, and, again, in 1840, the
excavations of the fortifications, were, in each instance,
followed by an outbreak of characteristic intermittent fever.
Irrigation of low-lying districts without proper drainage ; for
example, in some of the irrigated districts in California, and
in some places in Punjab, India, has been followed by an
outbreak of malaria or an increase in the severity of the
cases. The disease is said to prevail mainly in plains and
valleys ; and it appears that the frequency of its occurrence
diminishes with the elevation above the level of the sea ;
and even immediately above plains made desolate by malaria,

salubrious regions are often found.   For   instance, the
district of Norma, on an   abrupt rocky elevation about 1,500
feet above the Pontine marshes, enjoys a most salubrious
atmosphere.   Nevertheless, as already stated, malaria may
exist in the mountains ; for example, on the Eastern Slope
of the rocky mountains.   It is found at an elevation of 6,500
feet, and in the Peruvian Andes at 8,125 feet.   Grassi has
seen a malarious district near Calico at the height of 8,450 feet ;
and the disease has been observed at considerable elevations
in other parts of Italy.   In India, on the Himalayan ranges,
at the height of 13,000 feet the disease is prevalent, and it
is very excessive at the height of 5,000 feet ; Kangra Valley,
which is situated at a considerable height, malaria is endemic
all the year round, the inhabitants of the surrounding places,
for instance Mundi, are very much infested with malaria.

The literature of malaria affords numerous examples
of circumscribed endemics of that affection.   One of
the best known is that which occurred near the city of
Sanegallia on the Adriatic.   In the city which is famous
for its beautiful shores and for the magnificent hills about
it, in which there are schools, hospitals, and other public
institutions, and which is visited in the summer by crowds of
bathers, malaria is unknown, as it is also in the surrounding
country, as well as in the neighbouring hills where there are
numerous cottages, villas, and houses inhabited the entire
year.   But there is one very limited area of malaria,
which is quite grave, because of the number of cases, as well
as of the severity of the disease in those attacked.   This
endemic is situated without the walls in a little suburb
consisting of a row of houses, in some places double, along
the left bank of a large drainage canal, constructed for the
purpose of carrying off the excess of water coming from the
hills, and conducting to the sea, the overflow from the river
Misia.   During the hot season the flow of water in this
canal ceases ; but, in consequence of irregularities in its bed

and banks, there remains numerous pools and stretches of stagnant water, the surface of which is covered with aquatic plants. The canal is deep, and in the upper parts its irregular banks are covered with vegetation, while in the lower parts its bed widens out as it nears the sea. Spanning the canal are four bridges, the one nearest the sea being for the railroad. Now, the malarial endemic is confined to the houses situated along the upper part of the canal, very many of the inhabitants of which are sufferers from malaria, those sleeping in the lower stories being first attacked and those in the upper rooms, whose windows look out on the canal, next. This last-mentioned fact is particularly noteworthy, as no cases of malaria were found among those who lived in the upper room facing the street, which runs parallel behind the first row of houses. Furthermore, it is interesting to observe that a family of six persons occupying the upper story of one of the houses on the bank of the canal, the windows of which, however, looked on the street, had remained free from the disease; but, early in August, 1897, this family was obliged to remove to the lower floor of the same house, on the canal side, and after having been there for fifteen days, every one of the six members of the upper rooms which had been vacated by this family continued to be in a healthy condition. At some points the houses along the canals formed a double row, while at others there is but a single row, this being sometimes on the canal side of the street, sometimes on the other side. Now where the row on the canal side is interrupted, the inhabitants of the other row suffer from malaria, but there are no cases to be found, where there are houses in rows on both sides, amongst those in the dwellings on the further side. There are, with the exception of the houses mentioned, others visited with malaria either in the surrounding country, or in the city, or in the hills; and even, as just mentioned, there is no malaria in the rooms of the houses along the

canal, the windows of which look out on the street
behind.   There is also no malaria in the houses along
the lower part of the canal where the sea enters for a
short distance ; indeed, some of these latter are rented
even by summer visitors.   Along the railroad, as well as
among the labourers in a large sugar refinery, the disease
does not exist.   In the case of this well-defined endemic,
malaria occurs in all its forms.   In the spring we find only
the distinctly *intermittent* fevers, specially *tertian ;* but in
the summer and autumn the *æstivo-autumnal* infection pre-
dominates, and cases of pernicious fever also occur ; in
winter there are the relapses, the anæmic and other sequelæ
of infection.   The presence of various species of malarial
parasites, corresponding to the clinical forms observed, is
revealed by microscopical examination.   The various febrile
types are encountered amongst those occupying the same
house, and even the same room.   It is clearly evident from
this description of such a markedly circumscribed endemic
of malaria, in which we find all the forms of infection, as
also in other centres of grave malaria, the Pontine marshes,
for example, what are the telluric conditions necessary to its
development and maintenance.   These conditions consist in
the formation, during the summer, in the bed and banks of
a canal, of small collections of stagnant water covered with
a layer of vegetation, surrounded by mud and shaded by
the rank vegetation of its bank.   Here there are no extensive
marshes, nor even stagnant ponds, but only puddles in
which plant decomposition takes place.   Now, in these
stagnant pools the *larvæ* and *nymphæ* of the mosquitoes,
which infect the houses of the wretched sufferers from
the fever, find a suitable nest.   That the telluric conditions
mentioned were the true determining causes of the malaria,
was demonstrated by the fact that this latter, running
into the autumn of 1897, did not re-appear in the summer
of 1898 when these conditions had been removed by a

process of natural sanitation. Torrential rains and floods occurred during the autumn of 1897 throughout that region, carrying away much of the sediments in the canal, deepening it by from two to five yards, and uncovering the timbers of the old bed; the flood also wore away the banks smooth, and even undermined some of the houses. The consequence of this was that in the summer of 1898, the water of the sea entered the canal which was kept clear by the ebb and flow of the tide. Not a single case of malaria occurred among the occupants of the houses infested by the fever during the previous years; the mosquitoes almost entirely disappeared, and it was only specimens of *Culex* that were to be seen. Another very important fact is forthcoming from the study of this circumscribed endemic, namely, that endemic malaria remains fixed in the place where the telluric conditions are favourable, and does not spread to any distance, even horizontally. Indeed, this intense and grave malarial endemic was confined for years and years to the few houses whose doors and windows looked out on the upper portion of the canal, where the stagnant pools were located. One gate of the city is but a short distance from the canal; and from the same part is seen one of the bridges crossing it. Immediately within the gate is an asylum, the hospital, and many houses, in all of which malaria is unknown; and of the city guards who are stationed at the gate from early morning till late in the evening, none can be found who has ever suffered from intermittent fever. It is evident from this that malaria is not carried by the winds, but that it is joined to the conditions of the place where it is located. Furthermore, as those who suffered at Sanigallia drank the same water as the occupiers of the immune houses, it is evident that the drinking water cannot be the vehicle of infection. Guided by the two great discoveries, that of the parasite in the blood, and that of the malarial mosquitoes, not only is it possible to study more accurately the

endemiology and *egographical* distribution of malaria, but *pandemics* of the disease will be better understood than heretofore, and the reason for the affection being unknown in certain places where all the conditions favourable to its development appear to exist. The study of the *meteorological* and *telluric* conditions existing in places devastated by malaria, specially of the second named, will be much easier in the future than in the past ; for, as it is now known, that the malarial parasite does not live free in the soil, but that it enters the bodies of certain species of mosquitoes, the problem will be greatly simplified. Finally the cultivation of many marshy, malarious districts has been followed by a marked improvement in the sanitary condition. The planting of trees has been supposed to have a particularly good effect, possibly because of the drainage of the soil which is thus accomplished. For some time it was supposed that certain trees, particularly the *Eucalyptus Globulus* had an almost specific effect in protecting the neighbourhood against malarial fevers. The advantages of this particular tree have been much exaggerated. Malarial fever never originates at sea. Those cases which have been reported date their infection, unquestionably, to some period before the voyage.

CLIMATE.

For the development of malaria, heat is one of the factors of cardinal importance. This is evident when we consider that the disease rarely extends beyond 63° to 64° of North latitude, and 57° South latitude ; and that, in proportion as we pass from these limits towards the equator, the disease progressively increases in both prevalence and virulence. Hirsch sought to determine exactly the northern limit of malaria, but found in individual malarious centres great differences in temperature and latitude, and demonstra-

ted that it was not the mean annual temperature that should
be taken into account, but the mean summer heat. It is
between the isothermal lines of 59° and 60° 8' F. that he
places the northern limits of the disease. The significance
of temperature is also apparent from the fact that, while
malaria in the tropic where it prevails endemically presents
more oscillations in relation, particularly with the dry and
rainy seasons, in temperate regions it is specially in the
summer and autumn that the disease prevails ; and, again, in
those parts where all the varieties of malaria are found, it is
only at the seasons that we see the grave and pernicious
forms of the disease. Thus, in the malarious parts of the
Roman Campagna, malaria occurs only in its milder forms,
chiefly simple *tertian* in the spring, while the grave forms
constituting the *æstivo-autumnal* endemic begin after the first
extreme heat of summer, usually in the month of July, and
continue with oscillations during the summer and autumn,
the endemic being more or less prolonged according as the
cold comes late or early, but usually ceasing abruptly about
the end of December. In winter we observe *relapses* of
the infection contracted in the summer and autumn ; and
these, though they occasionally continue until summer,
usually grow milder and milder and cease, as a rule, in the
spring. The last cases of primary attacks, observed at the
end of the season of malaria, may not declare themselves for
many days after the possibility of infection has passed.

SEASON.

Malaria exists usually throughout the year in tropical
countries, but it is almost always more severe in the summer
and autumn. As one approaches the temperate climate, the
cases in winter and spring become very rare along the
eastern coasts of the United States of America, just as in
Rome, the cases in the winter are very few, while with the

spring a certain number of infections begin to appear; it is not until July that the real malarial season begins, its height being reached in the months of August, September, and October. The variations in the occurrence of the disease according to the season of the year is well instanced by the number of cases treated at the author's dispensary between January 1st, 1902, and January 1st, 1906. In January there were 9 cases; 8 in February; the same number in March; 17 in April; 21 in May; 18 in June; 38 in July; 66 in August; 122 in September; 120 in October; 38 in November; and 25 in December, making a total of 490 for the twelve months in question. The mildest types of infection are seen in the earliest cases. Thus, in the spring the first cases are usually *tertian* infections. As the season advances, double tertian infection become more frequent, while at the height of the season the majority of cases are of the *æstivo-autumnal* type, the most severe form of malaria. This observation of the variation of the types of the fever is a very old one. It has long been supposed that the early cases of fever in the winter and in the spring represent, *in toto*, relapses from infections of the preceding autumn, the fevers of first invasion beginning only with the summer months. Various analyses of cases have shown, however, that while the proportion of the fevers of first invasion is less in the spring than in the summer months, yet they do occur at that period. Dr. Ballori has drawn up a table, showing the number of malarial patients he received each month during the years 1889—96 in the Santo Spirito hospital at Rome, from which the close dependence of the malarial infection upon the seasons is apparent. It demonstrates that most of the cases of the disease occur in the months of July, August, September, October and November In December the number of malarial cases is markedly less, and continues to decrease progressively, through the winter, during which time only patients with relapses

are received. In the months of May and June there is more or less noticeable increase marking the spring endemic, but there is a striking and sudden increase, denoting the beginning of the æstivo-autumnal endemic, in July. It is not everywhere that this relation between the number of cases and the months of the year is to be observed. In some malarious districts in Italy the maximum of the *æstivo-autumnal* endemic occurs in the autumn, specially in September and October, and in other places even in November and December. Furthermore, in the same place, the period of maximum prevalence may vary in different years. In the Roman Campagna, in the year 1898, it was in November and December, and even in the first part of January, that the greatest number of pernicious fevers occurred. The effect of heat does not declare itself immediately; and there are other intermediate factors concurring in the production of the disease. Thus, while it is certain that the æstivo-autumnal endemic always develops after the first strong heat of summer, it is also certain that it may be prolonged in the late autumn when the temperature is lower than that of June in which few or no cases of primary æstivo-autumnal infection are seen. Furthermore, the gravity of the malarial endemic in any year is not always in direct ratio with the height of the mean temperature for the warm months. The latter may even be lower than usual and the former extremely severe. The life of the malarial mosquito has to do with this course of the malarial endemic relative to the seasons. With the first intense cold some of the mosquitoes die, others hibernate. In the spring the latter emerge from their hiding places, and deposit in stagnant water their eggs, whence comes the new generation to which others succeed in the summer and autumn. Researches are still being carried out with the view of discovering the relationship between the development of æstivo-autumnal endemic and what happens to the mosquitoes whereby they become infected. It is now

known that in the late autumn the malarial mosquitoes, very many of which are infected, seek shelter in the houses; the curious fact of their being true house epidemics of the disease, and the great liability to infection at this time can thereby be explained. The origin of the æstivo-autumal endemic is not yet understood ; but doubtless we shall soon know that the daughter mosquitoes have inherited from their mothers the infection, which requires an elevated temperature in order to develop, and be transmissible to man : if the daughter mosquitoes infect themselves by sucking blood still containing crescent forms, and if these develop in them later when the temperature of the air permits, and also, if the mosquitoes become infected in some other way, as, for example, by sucking the blood of other animals. The possibility of a seasonal polymorphism of the *hæmosporodia* of human malaria, that is to say, of the transformation of the spring parasites into æstivo-autumnal ones, has been suggested by various observers.

RAIN.

Thus appears to have an important influence upon the production of the disease. In tropical countries, where the rainy season alternates with the dry, we find the curve of malarial morbidity correspond very nearly to that of the rainfall, and in such a way that the maxima of the first follow those of the second at an interval of about a month. It is the general belief that in climates that are temperate an injurious influence is exerted by the summer and autumn rains ; and also that a very rainy spring is followed by a malarial season, more serious than usual, by reason both of the number of cases and their gravity. Rain appears to influence the development by action as an occasional exciting cause of the development of the infection in the human beings, and also by favouring the telluric conditions necessary to the production of the disease, or, more exactly,

of the life of the mosquito. It is by the heavy rains of the spring that there are formed numerous stagnant pools and marshes where the mosquitoes can deposit their eggs ; and similarly the rains of the summer and autumn keep these pools and swampy places from drying up. But the amount of rain must not exceed a certain limit; for, when heavy showers follow each other at short intervals, the exit of the winged insect from the *puparium* may be prevented. Furthermore, the influence of rain may, as regards its influence in the production of malaria, be nullified by several factors, as, for example, when a strong wind is blowing in the intervals of the showers so as to dry the soil quickly. To this action of rain we may add another, namely, that of favouring the manifestation of the infection in a person who has already got the germ in his body. This second effect of rain is manifested very quickly, while the first mentioned requires considerable time, a month, according to experiments in hot countries, which is a period corresponding to the incubatory stage plus the aquatic life of the mosquito.

WINDS.

There is much that has been brought forward to suggest that the infective agent of malaria may be carried by the wind ; but all are not agreed as to this probability. Some have affirmed that the disease may be transported to long distances, even from one continent to another across the sea, by the agency of the wind ; but others strongly object to this hypothesis, and others, again, look upon the wind as actually doing good by dispersing and destroying the malarial germs. The first of these opinions is held by Lancisi, who, in accordance with this belief, would not permit the cutting down of groves, even in the plains, maintaining that they acted as filters purifying the air passing through them the emanations from the marshes. But this view is opposed by so many and such convincing facts, related by numerous observers

that we can no longer admit any connection between the wind and the diffusion of the malaria. It is sufficient to recall the fact that no ships anchored even close to the shore of exceedingly malarious districts, the members of the crew never suffered from malaria so long as they remain on board the vessel, but that may acquire the disease, and perhaps succumb to it, if they go ashore and remain there even for a single night. For instance, Mannaberg says, Vincent and Burot affirm that in the Madagascar campaign of 1895, while the French troops were disseminated by the fevers, the sailors who remained for months on board the ships, hardly 300 yards from the shores, escaped. Then, again, in very circumscribed malarious districts the infection may be intense, but it will remain within these narrow limits for years and years without spreading itself in any direction. In cities like Rome, situated in the midst of an eminently malarious region, even during the season when numerous malarious cases are admitted from the neighbouring Campagna to the hospitals, the inhabitants never contract the disease. Why malaria cannot be transported by the wind can, as a rule, be explained, if it is true that man acquires the disease only through inoculation by infected mosquitoes, by the habits of the latter. For, as a matter of fact, when the wind blows the mosquitoes conceal themselves in the grass or the leaves of the bushes, and it is only when the wind dies down in the evening they they take themselves on their wings, sting men and animals, and invade the houses. Furthermore, in no single instance were any species of *Anopheles* found after repeated and careful search in the gardens, within the city of Rome, situated at a very short distance from the malarial Campagna; and the observations of Grassi demonstrate positively that malarial mosquitoes are not transported by the wind, for he found *Anopheles* in circumscribed malarious districts, but was unable to discover any at all in the neighbouring regions that were free from that febrile affection.

ALTITUDE.

Times out of number it has been observed in malarious districts that the dangers of infection are much greater close to the ground. Sleeping upon the ground is held to be particularly dangerous in such localities.

TIME.

It is said that infection takes place more readily by night than by day in infected districts.

DRINKING-WATER.

As a source of malaria many have laid, and still do, great stress upon drinking water. The experiments, however, of Celli, Marino and Zeri who caused individuals to drink large quantities of water which was obtained from the most malarious districts, without any bad effects, and of Grassi and Fletti, who fed individuals upon dew collected from malarious regions, with similar negative results, are strong arguments against this idea.

OCCUPATION.

The susceptibility to malaria is considerably influenced by occupation. Soldiers and poors who sleep upon the ground in malarious districts are particularly prone to contract the infection. While those whose work takes them into the insalubrious countries are apt to take the disease ; labourers in the cities are exempt, with the exception of those who live in houses on the outskirts of the city overlooking the open country. But even among the field labourers we must distinguish between those who remain in the country only during the day time and those who pass the nights there ; the latter being more subject to the malarial attacks ; also between those who work only in the winter and spring, who do not take the disease or only in a mild form, and those who toil in the fields during the summer and autumn, who suffer more frequently and often from the pernicious fevers. In the Roman Campagna, for example

the labourers who harvest the hay in the spring are free from infection, or, at most, suffer only from a simple *tertian* fever; while those who harvest the grain, and specially those who thrash it and engage in other of the autumnal works, pay a heavy tribute to malaria. Besides agricultural labourers, those also are subject to the malady who are obliged to work at ditching, excavating, and other tasks, *e.g.,* railroad construction, the building of fortifications, the diking of rivers, and so forth. The disease also takes hold of those who pass days and nights in malarious regions, *e.g.,* brick-makers sleeping or staying in kilns, soldiers, carters, hunters, and those who have village works.

AGE.

Except in so far as the very young and the very old are less to be exposed to the infection, age appears to have no predisposition to the disease.

SEX.

The predisposing effect of sex is also nil in itself though men are apt to be more exposed to the disease than women.

RACE.

There appears to be a relative insusceptibility to malaria in many infected localities amongst the natives of the Tropics. This appears to be specially true as regards the Negroes, the Indians in some places, and the Arabs. The degree of this insusceptibility varies, however, in different localities, according to different observers. The susceptibility of the natives of the tropics is only one-third of that of the whites.

DIET.

Residents in malarious regions believe that the fever may be caused by acts of imprudence in diet, such as the eating of excessive fruits, specially unripe ones. Although this is not strictly true, we can readily understand how the organism may be rendered less resistant to the action of the parasite.

Any indiscretion in diet is followed by gastro-intestinal disturbances, specially by a debilitating diarrhœa, when circulatory changes caused by digestive disorders already exist, perhaps also the localisation of the parasites in the capillaries of the gastro-intestinal mucous membrane, as occurs in. choleraic pernicious fever, may take place more readily. The susceptibility of the organism to the development of the specific poison is intensified by all such debilitating factors, as excessive toil, specially in the sun, mental disturbances, and insufficient food.

TRAUMATISM.

It has often been asserted that, where a previous attack of malaria has existed, injuries of various sorts are particularly likely to be followed by a relapse of the disease. It is often said, for instance, that an injury to the spleen in a patient who has formerly had malarial fever, may call forth a relapse. With regard to the effects of traumatism, observations made on thousands of cases have not given any positive answer, while the complications of malaria with other acute diseases have been, perhaps, rather surprisingly infrequent. It seems reasonable that trauma or operation by reducing the vitality of the patient, should render him more susceptible to a fresh malarial infection, or more liable to a recrudescence of an already existing process. In many hospitals, however, in malarious districts, not a single case of post-operative malaria has, during the course of many years, been observed; so that the hypothesis of many of the chills occurring under these circumstances, generally supposed to be malarial, being in all probability septic is a reasonable one.

IMMUNITY.

It is a well-known fact that many persons are immune from malaria and experimental malaria, and the same is

true of certain races, at least, the latter present a varying degree of resistance to the infection. Thus, Negroes inhabiting malarious regions in the tropics are less subject than white men in the same places to the grave forms of malaria, and, having once been infected, they are said to acquire a relative immunity more readily than the whites. All the observers do not subscribe to this theory of racial immunity. Some attribute to the blacks an almost complete immunity, but this, as recent observations have demonstrated, is an error: possibly the various races of coloured persons differ amongst themselves in this respect. According to Plehn, the natives of the Kamerun coast seldom have fever, and when they do, the febrile paroxysms never last more than a few hours; they rarely ask the Europeans for quinine, and usually recover spontaneously in a few days. But a change of residence deprives them of this relative immunity, at least temporarily. The Malays and the Javanese, according to Martin, whose observations were made in Sumatra, enjoy a certain degree of immunity, suffering from the most part from mild forms only of the disease; and the Tamils and Gorkhalis are still less predisposed to malaria, although they are chiefly workers in the fields. Amongst the inhabitants of different regions, however, even in the same race, there is often observed a varying power of resistance. For instance, it is known that in Italy the peasants of Venetia and of the Marches suffer terribly from malaria when they come to work in the Roman Campagna, while, it is said, the inhabitants of Abbruzzu and of the mountainous parts of Latium possess in general a greater power of resistance. The latter has been attributed to a natural selection effected by malaria upon the population, the custom of descending from their native mountains, during the season of agricultural labour, into the salubrious plains having been observed by the inhabitants of these regions for centuries. Evidence of great variability in individual resistance to infection, and

even examples of veritable immunity, are to be found among the fixed population of malarious regions. We have to distinguish a congenital immunity which may be a *family* peculiarity, and an *acquired* immunity, which, in the great majority of cases, is not complete but only relative. Before asserting the complete immunity of any given individual, we must be sure that he has lived a sufficiently long time in a place where grave malaria prevails. Indeed, we may sometimes see individuals, who have been for a year or even longer in malarious regions without contracting the disease, suddenly fall victims to a grave infection when they had come to regard themselves as perfectly secure. It is necessary also to be certain that the person in question has actually been inoculated with the malarial germs. Indeed, for a long time they have escaped infection, who have always carefully avoided sleeping out of doors or with open windows, who have always slept under a mosquito bar, who, in a word, perhaps, unconsciously have always so conducted themselves so as to avoid being stung by malarial mosquitoes. In the case of white persons it is very seldom that we come across any instance of congenital immunity, yet they are to be found in all malarious districts if sought for. Many appear never to have had the disease and exhibit no splenic enlargement. The descendants may have inherited this immunity from them; and many such cases are on record. Acquired immunity is, however, much more common. It is often that one observes individuals who suffer from malaria, during the first year of their sojourn in the infected region, for many months, usually from the summer or the autumn to the spring of the following year, but after that remain well, having a fairly healthy appearance, and being capable of considerable work; but on examination they are found to be suffering from enlargement of the spleen, often of considerable size. There are also persons who, during a residence of many years, even 15 or 20, in a markedly

malarious region, have never suffered from attacks of typical malarial fever, but are troubled from time to time with a slight feverishness which they attribute to an imprudence of some sort, but which is probably a very mild malarial attack excited by overwork or exposure. These individuals look fairly well, and they preserve their strength and ability, to work often to an advanced age, but examination shows enlargement of the spleen. In the first of these cases there is more or less a complete acquired immunity following a series of febrile attacks; in the second, the individual is endowed from the first with a marked power of resistance, in consequence of which the infection has never run an acute or grave course, such as it usually does in new arrivals in malarious places, but has rather been chronic from the beginning, and during this time the subject has been gradually increasing his initial resisting-powers until he finally acquires quite a notable degree of immunity. It should be stated that examples of this sort are to be seen among the permanent inhabitants of the malarious regions, only in that class of workers, who are well-fed, relatively well-housed, and are not obliged to work, but usually pass the day on horseback, directing the labourers and superintending the work. It is only under the most favourable conditions that acquired immunity can be developed in an ordinary labourer : certainly it is very seldom seen in persons of that class. Though in the rare above-mentioned cases there is established a relative immunity of great practical value, in the vast majority of instances the organism acquires gradually a certain degree of resistance to the infecting agent ; but this resisting power is not sufficiently strong to prevent relapses from time to time which finally induce a *cachectic* condition. Although, at first thought, the application of the term acquired immunity from cases of this sort, in which the individual is reduced to such an unenviable condition, does not seem justifiable, yet we find many proofs that such subjects are rarely

more resistant to the action of the malarial germs than new
arrivals who have never had the fever. For example, it is seen
that pernicious attacks are almost always primary, or at least
occur with the first relapse. It is common to find the spleen
very soft, and but slightly enlarged, at the *autopsy* of one
who has died of a pernicious fever ; and, on the other hand,
it is rare to find the characteristic parasitic conditions of
pernicious infection in an individual with a pronounced
chronic enlargement of the spleen. It is perhaps correct
to say that the majority of those who become *cachectic*, after
a long sojourn in a malarial region, do not die of malaria
but of its consequences, and generally of complications, such
as pneumonia, and the like. At the autopsy of such a
cachectic subject who has remained up to the end of his life
in a malarious district, a recent malarial infection is excluded
by the fact that the enlarged spleen is usually found of a
bright red colour, and without a trace of *melanosis*. The
study of the ordinary course of malaria, and both in those
who leave the district after having acquired the fever, and in
those who, remaining there, are continually subject to re-infec-
tion, furnishes the proof that a relative immunity is gradually
established during malarial infection. This fact is also to be
observed in tertian and quartan fever ; for, as we know,
if the treatment is instituted properly at the beginning of
the disease, we usually succeed in reducing it to a minimum,
or even averting entirely the relapses ; while in quartan
fever the groups of attacks follow each other with the greatest
obstinacy, separated by longer or shorter intervals of apyrexia,
and, even when the patient is living amidst circumstances of
the most favourable kind, the infection in some cases dies out
only after many years of existence. The ingestion of *quinine*
might be supposed to be the direct cause of this. Indeed,
most patients succeed in overcoming the fever, after a certain
number of attacks, with the drugs ; then after a certain
period of *apyrexia*, the relapse occurs, the mildness of which,

compared with the primary attacks, might be thought to be due solely to the fact that the infection has been attenuated by means of the remedy. It may be affirmed with certainty, that this course is owing not only to the treatment adopted, but in great part to the modifications occurring in the human organism during the existence of the infection. Indeed, if we refrain from giving quinine to patients not suffering from a grave form of the disease, we find that, after a certain number of febrile *paroxysms*, the upward temperature curves tend to become less marked, and a spontaneous recovery takes place. But this cure is temporary only, and after a variable interval the fever returns, usually in milder form. Again, not only is the fever less pronounced, but all the effects upon the organism of the malarial poison manifest themselves in the successive relapses in continually lessening degree. For example, we find that patients, under equal conditions as regards the quantity of infection, become less anæmic in the relapses than in the primary attack. It is probable that the patients of malaria were cured before the discovery of the properties of the *cinchona bark* in this way. There can be no doubt that the spontaneous cure of the disease is primarily connected with the modifications which the infection itself produces in the human organism. Indeed, we cannot explain it at all, unless we admit either a progressive attenuation of the parasites until they have lost gradually their pathogenic action and their capacity for multiplication, or a progressive increase in the patient's power of resistance to the pathogenic action of the parasites; in other words, an acquired immunity. While not absolutely denying the pathogenic action of the parasites may be weakened in the course of time, we yet cannot attach very great importance to their attenuation. Indeed, patients with chronic malaria, even when they remain permanently in a malarious region, where they are continually subject to re-infection with fresh virulent material,

do not, as a rule, suffer from the grave forms of malaria as do the new arrivals. Furthermore, experiments have demonstrated that, when blood, containing very few parasites taken from a person who has spontaneously recovered from an attack of malaria, is injected into a healthy person, a grave form of infection may be induced in the latter. It is therefore the organism of the patient himself which prevents the parasite from developing its pathogenic action, and not the parasites which have lost of themselves their power of exciting the disease. We are forced to the conclusion that the defensive capacity of the organism has been weakened by the action of cold when a patient, say, one suffering from a quartan fever, in whose blood the parasites regularly pass through their life-cycle without inducing *pyrexia*, is seized anew with febrile paroxysms, in consequence of the action of some occasional cause, such as a cold bath. It is very evident, then, that certain changes take place in the patient during the febrile attacks, by means of which he acquires an immunity from the effect of the specific cause of the disease; but this immunity, as is the case also in certain other infectious diseases, is of brief duration, and when it is weakened the relapse occurs; this confers anew upon the patients an increase of his period of apyrexia. The fact that even re-infection does not, as a rule, take on a grave course, and that there is a diminishing intensity of the successive seizures, can be referred to the persistence of a part of the acquired immunity after every apyretic period. The usual course of the malarial infection can probably be explained in this way. The results of the researches made up to the present time do not allow of the analysis of this acquired immunity of malarial subjects in the same manner as has been done in the case of some other infectious diseases. Attempts to confer immunity upon man artificially have hitherto failed; but we must remember that the experimental study of this question in the human being is attended with

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great difficulty. It is evident that the practical value of this relative immunity acquired by malarial subjects is very small, even after a long course of infection; for if we expect the small number of persons who become immune after a few months of fever to such a degree that they can remain in the malarious region without suffering from further attacks, most subjects acquire this relative immunity at the cost of a chronic infection or *cachectic* condition. This causes progressive degeneration of the races living in regions of intense malarial prevalence, and hinders the natural selection through the action of which we might, *à priori*, look for the creation of an immune race. The fact that the agricultural population of malarious regions is constantly being thinned out and must be constantly recruited by labourers coming from non-malarious districts, and also that the above-mentioned delection in the case of the white races does not act in such a way as to produce practically useful results, has been demonstrated by very long experience. It is a matter of doubt whether a certain degree of immunity from malaria is conferred by other affections It has been widely believed that some skin-diseases afford protection against the fever. This is asserted by many in the tropics, specially in the case of *lichen tropicus* and *tropical furunculosis* —infections due, it is alleged, to the *staphylococcus pyogenes aureus.* The same opinion is held in India, but admitting the correctness of this observation, we may yet ask whether we have to do here with a true immunity conferred by the cutaneous affection, or whether these patients escape malaria because, owing to the condition of their skin, inoculation by the malarial germs is impossible. It is probable that, if the infected mosquitoes do puncture the skin, the condition essential to their development is not existing for the malarial *sporozoites* in the blood vessels of the infiltrated and inflamed dermic area ; for it is said that those subjects are exempt from malaria only so long as the disease of the skin lasts.

MANNER OF INFECTION.

The nature of infective agent in malaria has been demonstrated by the researches of Laveran and others while its specific action has been abundantly shown by clinical observation and inoculation experiments. *Three* modes of infection have been suggested, *viz.*, directly from the external world, subcutaneous or intravenous inoculation of human blood containing the parasites, and by passing through the placenta of a malarious mother to the circulation of the fœtus. These, it is necessary to consider at some length.

(1) That the natural way of contracting malaria is by inoculation is obvious from what we have said regarding the life-cycle of the malarial parasite in certain species of mosquitoes. If it is admitted that the facts above-mentioned concerning the life-cycle of the malarial parasite in the Anopheles represent practically the entire biology of these beings outside of man, then we may assert positively there can be no other. The conclusion that a man acquires malarial fever solely through the bites of certain species of gnats by means of which occurs inoculation of the malarial *sporo-zoites*, would be the logical and necessary consequence of such premises. This conclusion, which is founded upon a series of facts tending to exclude the possibility that the infection may take place in other ways, can be maintained, in spite of the fact that we cannot positively deny at the present time that the malarial parasites may exist under other forms than those now known to us. Independently of what we know regarding the biology of parasites within the bodies of the *diptera*, this renders the study of the problem as to how fevers are contracted; that is to say, it is necessary to see what *clinical* and *epidemiological* experience in malarious regions teaches, and then to set forth in detail the experiments upon which the theory of inoculation is based. Such an exposition is more necessary, since, even at the present

time, many authors, while recognising the importance of
mosquitoes as vehicles for the transportation of the malarial
organism, yet refuse to admit, that inoculation is the sole
mode of infection, and incline to the belief that, as Lancisi
held, there are multiple channels of ingress of the malarial
germs.   This opinion is now being rapidly abandoned.
There were three theories, for long entertained, as to the
mechanism of infection by the malarial germs, viz., the water
theory, the air theory, and the inoculation theory. The latter
that the malarial germs are inoculated into man through the
agency of mosquitoes, is the only one which has up to the pre-
sent time been demonstrated experimentally. Now, regarding
the water theory, the hypothesis that man may become
infected with malaria by drinking water from marshy places,
is supported by many facts adduced by its advocates.   Thus
it has often been affirmed that of certain individuals living in
a special locality under otherwise identical conditions, but
drinking water from different sources, some were attacked in
large proportion by malaria, while others were spared by the
disease.   In certain insalubrious localities it has sufficed to
provide a pure water-supply to the inhabitant, water from
stagnant pools having previously been used for drinking
purposes, to cause the malarial fever to appear.   Examples
have been cited of travellers who, while passing through
malarial countries, had succeeded in preserving themselves
from the fever by drinking only boiled water, while large
numbers were attacked who did not take this precaution.   In
very healthy places the fever might be contracted when water
brought from an unhealthy place was used for drinking,
and those individuals who were most apt to take the fever
were the ones who had consumed the greatest amount of
suspected water.   That many of the facts upon which their
arguments are based are not above criticism is now recog-
nised by many advocates of this theory advanced by Laveran.
Indeed, many of the facts themselves are not definitely

established, and are rather vaguely stated. In many cases, no proof is given that the fevers which followed the ingestion of the alleged unhealthy water were truly malarial. Others of the facts given are open to various interpretations. For example, when it is affirmed that the intensity of the malaria diminished after a district had been supplied with pure water, we must remember that this fact may have been due to a general improvement in sanitation ; malaria, we know, retires before the progress of hygiene and civilisation. When we hear of individuals living under identical conditions, of whom those acquired malaria in the greatest number who were forced to drink water from stagnant pools, we forget that this very fact itself shows that the conditions were not really identical. We cannot exclude the possibility that those who drank the stagnant water may have been exposed more than others to the occasional causes of malaria, or offered less resistance to the germs of the disease. Furthermore, the possibility that the drinking of stagnant water may facilitate the development of the parasites which have already, as we know happens through the influence of poor food, chilling of the surface, and debilitating conditions, cannot be excluded. The results of experience in such places as the Roman Campagna may be opposed to these facts. Many localities, indeed, are known in the environs of Rome which are exceedingly malarious, yet in which the inhabitants drink the same excellent waters as those supplied to the city itself. In other places, Ostia, for example, good drinking-water has been introduced with no improvement in respect of malaria. In various other parts the study of epidemic of the disease leads to the inevitable conclusion that water is of no importance as a vehicle of infection. Experiments, with a view to ascertaining whether water taken from a malarious district to absolutely healthy ones could convey infection to healthy individuals drinking it, have been carefully carried out in various regions. Celli, for-

example, caused healthy persons in the Santo Spirito hospital to drink water for several days which had been collected in the Pontine marshes and from stagnant pools in the suburbs and environs of Rome, but with negative results. Negative results have also been obtained from other experiments. The question has been studied in India by Ross, who adduces a single fact in favour of the water-borne theory of the disease. Led by the hypothesis previously mentioned, according to which the mosquitoes, having taken in human blood charged with malarial parasites, go to deposit their eggs in water and die there, whence the infection of the water itself, he had a person to drink in which there were dead mosquitoes containing malarial parasites. Eleven days later, the subject of the experiments had an attack of fever which lasted three days and ceased spontaneously, no relapse following. In the blood of the patient, Ross declared that he found many annular forms of the plasmodium. But, in other individuals, in whom he repeated the experiment, there followed no fever which could be certainly called malaria. This renders the value of the first *nil;* and no one has yet been able to propagate the disease by the ingestion of water from swampy malarial places.

At one time both the profession and the laity believed in the air theory ; and the advocates of it maintained that the free life of the parasite is passed in the soil or in the water of marshy places, whence it passes into the air and infects man through the channel of the respiratory organs Numerous researches have been made with the aim of discovering the germs in the so-called malarial material, but all without results. Among the most recent of these experiments we find those of Grassi and Calandraccio, who held, some years ago, as a definite fact, that the malarial parasites were *rhizopods* or forms repeated to them ; they, therefore, sought for them among the members of this group which are found, in their free existence, in the so-called malarial materials, such as uncultivated

fields, made land, rice-fields, and so forth. They vaunted the theory that the malarial parasites were to be found in the genus *amœba*, in its wide sense ; and they assumed that certain amœbæ, living in a nonparasitic condition, became encysted, were carried into the air, and so entered the body of men, there developing and taking on characters somewhat different from those of their ancestors in the non-parasitic life. In support of the air-borne theory, it cannot be cited, and for the reason that this assumption is overthrown by the result of modern researches, various observers have found considerable difficulty in explaining by the air-borne theory certain of the best attested epidemiological data of malaria. It does not, in fact, satisfactorily explain how the germs enter the air from the soil, to which latter epidemiologists in general assign the origin of the miasma ; nor does it explain why at different hours of the day there is such a variation in the change of malaria in the atmosphere, nor, again, does it explain why the disease is not carried by winds, or at least is not notably so carried. To the theory that the germs could rise into the air from the soil along with the dust, we may object that malaria does not act like a disease caused by the inhalation of dust ; and, furthermore, that the days of greatest danger are windless, when less dust rises ; and specially on the still warm days following a rain in which no dust rises from the damp earth. If it were alleged, on the other hand, that the germs pass into the air from humid soil, then it would be necessary to assume— this supposition being altogether arbitrary —that something occurs with great facility, and, as a rule, in the case of malarial germs which, in that of ordinary bacteria, has never been satisfactorily shown to take place. Hirsch, Tommassi-Crudeli, and others have asserted that the wind transports malaria only to a very short distance, if at all, and that practically it plays no part in the diffusion of the disease. If the emanations from the Pontine marshes were the cause of the malarial

fevers in the Roman Campagna, as Lancisi believed, then it is impossible to understand why the cities of Velletri, Genzano, Ariccia, Albano, etc., which lie between Rome and the marshes, and ought to receive first and in greater concentration the noxious emanations transported by the wind, should be entirely free from malaria. If the latter could be transported to a considerable distance by the winds, we cannot understand its presence in strictly circumscribed regions in various parts of the world. It is also worth mentioning that Tommassi-Crudeli called attention to the well-known fact that malaria rises but a short distance above the ground. Experience has taught the inhabitants of the Pontine marshes to sleep at night, during the fever season, on platforms raised, from 13 to 16 feet, on poles. Our author also says that the fact that the germs do not rise far above the plain, will explain the notable differences that exist with regard to malaria between Norma, Sermoneta, and Sezze, cities lying above the Pontine marshes. The sea-breeze which blows in summer in Rome does not bring danger, yet it passes over all the swamps on the coast. But it is not, says, Tommassi-Crudeli, that this breeze does not carry malaria in the direction of Rome, for it does carry it and in large amount; but it carries it while acting at the same time as a ventilator, that is to say, it scatters the germs in every direction, although it is a current of air of very slight velocity. Nevertheless, it is not easy to believe that a current of air, carrying every day, as he believes, as large quantity of malarial germs, does not fill the city with malaria; and it is a proper conclusion that it does not carry the germs of the disease at all, and that his argument is based on a false assumption. In short, the air-borne theory of malaria does not permit of a satisfactory explanation by epidemiological data; and, despite the most ingenious attempts at an explanation, it is scarcely possible to conceive how the winds do not transport the germs of malaria of those are present in the

air. On this theory it is impossible to explain the great differences as regards the danger of infection between walking and sleeping in a malarious region ; and also the fact which has been repeatedly observed, that the crews of ships lying on the most insalubrious coasts escape, only those men being attacked whose duties compel them to pass a large part of the time on shore. The insurmountable difficulties encountered in accepting the air-borne or the water-borne theories naturally lead us to think of some other mechanism by which the malarial germs may gain entrance to the human body, and more especially of inoculation. We are driven to this hypothesis partly by the exclusion of the two preceding ones ; partly by the fact that subcutaneous or intravenous injections of malarial blood is the only means by which hitherto malarial fever has been produced experimentally ; and partly by the analogy of human malaria, in a parasitological sense, to Texas fever—this being due to inoculation by a kind of *tick*. The probability of this theory was demonstrated by Bignami in 1896 ; he at the same time affirms that it readily and satisfactorily explains many facts that are difficult of explanation by the air-borne theory. Thus, admitting that malaria in mankind is the result of inoculation by mosquitoes, it is not difficult to explain why it is particularly not carried by the wind; it is also easy to understand why the danger of acquiring malaria is the greatest in the evening and the night. We see at once why the infection does not rise far above the ground. We comprehend readily the danger of sleeping in malarious districts; and finally, this theory explains perfectly the well-known prophylactic efficacy of mosquito nets in regions where malaria prevails. It likewise explains the efficacy of the prophylactic measure adopted, as the result of experience, by the inhabitants of malarious regions ; many of the precautions taken against the fever seem really to be taken against the attacks of the insects in question. All this, indeed,

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accords exactly with what we know of the habit of mosquitoes in malarious countries, which sting specially at night and during the evening, and do not fly far from marshy places where the proper conditions of their existence prevail. They hide during the day as to be out of the way of the winds. They are most numerous in places where malaria prevails. They disappear from places where sanitary measures have removed the conditions necessary for their existence, and do not fly to any great height above the ground. Bignami was led by these facts to the conclusion that malaria acts like a disease inoculated through the stings of mosquitoes. In order to verify this hypothesis experimentally, it was necessary to cause healthy men, living in a positively non-malarious district, to be bitten by mosquitoes transported from a place where malaria prevailed. After some fruitless attempts, these experiments have given positive results, the precautions being taken to capture adult mosquitoes in pronouncedly malarious regions somewhat late in the season, as the number of infected insects is much greater at that time than at the beginning of the season of malarial prevalence. The first experiments attended with absolutely positive results was carried out in the person of one Abele Sola, an inmate of the Santo Spirito hospital for the past six years, who suffered from a nervous affection, but had never had malaria. He offered himself voluntarily as a subject of the investigation. This was carried out by liberating, in a suitable room provided with mosquito bars, mosquitoes brought from Maccarese, a marshy place, famous for the intensity of its fevers. It is not necessary to describe these experiments in detail, as they are to be found in Bignami's work. It is sufficient for our purpose to observe that with these three new cases of malaria experimentally produced by the anopheles alone, the inoculation theory acquires a very strong confirmation. The individuals submitted to experiment have been few in number ; but it is to be noted that, whenever an attempt was made

under appropriate condition to excite the fever by inoculation, it was successful. The experiments have shown that very few punctures by very few infected mosquitoes suffice to give the fever ; a positive result has been obtained with only two infected insects, and it is quite certain that one alone would be quite sufficient. When we think of the enormous number of malarial *sporozoites* which can be found in the cells of even one tubule of a salivary gland of anopheles, this fact need cause no astonishment. This answers the objection advanced by many that there are malarious regions in which very few mosquitoes are found ; the number of the infected insects, and also their species, must be taken into account. It appears certain that a solitary specimen of anopheles may infect several persons. Indeed, there have been found *sporozoites* in the middle intestines of mosquitoes, which had bitten healthy individuals, and caused them an attack of malaria. In this case, therefore, even had the anopheles emptied the entire contents of the salivary gland at each bite, the insect would be capable of inoculating other persons with the fever, as the glands would again be invaded by other sporozoites from the middle intestines Finally, we may take it as proved that the only way in which man takes malarial fever is by inoculation effected by certain species of mosquitoes.

(2) Some of the older writers believed that malaria could be transmitted in the sweat, but this opinion we now know to be erroneous. Mannaberg says that Dochman considered that he had reproduced a malarial fever by inoculation with the contents of an herpetic vesicle occurring on a sufferer from quartan fever ; but this experiment has never been repeated, and the results lack confirmation. Inoculation with blood containing the malarial parasite will transmit the fever to a healthy individual. This fact has been experimentally demonstrated by Gerhardt, who saw a typical intermittent fever reproduced in an inoculated subject ; and

it has been corroborated by Marchiafava and Celli, and others who, by finding in the blood of the inoculated person the same parasites which were present in the blood of the patient from whom the material for inoculation was derived, leave the question no longer in doubt. Innumerable other investigators have done the same thing; and in this way has been forthcoming a confirmation of the doctrine of the multiplicity of species of malarial parasites. Furthermore, they gave results which were of great utility in the study of the doctrine of incubation. The transmission of the disease occurs equally whether the blood is taken during the apyretic period or during a febrile paroxysm, whether it contains young parasites or those in process of development, or whether it contains a sporulating form. In view of what we know regarding the biological significance of the crescent forms, it is not surprising to learn that the latter, when injected alone, do not transmit the disease   A subcutaneous injection alone is necessary to convey the infection to an inoculated subject; it is not necessary to inject the malarial blood into the vein of the recipient, as has been done in most of the experiments. It is not even necessary to inject several cubic centimetres, as was done especially in the earlier researches; a fraction of a cubic centimetre would suffice, and even less than one drop will do   Most of the experiments were made by injecting blood in the natural state, soon after it had been drawn from the patient's vein; but positive results have also been obtained with the injection of defibrinated blood, and of blood obtained with leeches, as well as of blood separated by centrifugation. In one case Di Mattei collected the blood from a case of epistaxis occurring in a malarial subject, in a test-tube containing sterilised and distilled water, at a temperature of 98·6° F., and injected a drachm of this mixture of equal parts of blood and distilled water; the subject inoculated had a fever 14 days later. If malarial blood is mixed with an equal

quantity of distilled water, the mixture being well shaken, a healthy man may be inoculated with the product, after it has been allowed to stand for an hour, with impunity. If blood rich in parasites is dried at the temperature of the air, and then dissolved in a tepid physiological salt solution, an injection of the solution will be innocuous, even when the blood has been left in the dry state for a very short time. It has been noted that blood also, which is filled with parasite, taken from a patient with pernicious fever may be injected without results After the administration of large doses of quinine, no morphological changes may be observed in connection with the parasites at the very moment of injection. It is only from man to man that it is possible to have a transmission of the infection through the injection of malarious blood; and then it is extremely rare for the inoculated person not to take the fever, a positive result being almost the constant rule. On the other hand, all attempts to induce malaria in various species of animals by injections of blood containing the parasites of human malaria, have been uniformly unsuccessful, even when the subjects of the experiments were animals which are subject to infection with hæmotozoa very much resembling those found in man. Various experiments, always negative in their results, have been made on various species of monkeys by Di Mattei (a macaco), Angelini (a cynocephalus sphynx), Richard, Fischer, and others. While positive results of the injection of malarial blood from man to man are almost constant, it is singular to find that contradictory results have been noted in experimental attempts to transmit the disease from one bird to another, even of the same species and variety. Grassi and Fletti, and Di Mattei have always had negative results, though Celli and Sanfelice claim to have seen the disease transmitted in this way in certain cases. In the " Zeitschrift für Hygiene " (XXXII, 1899) R. Koch says that it appears that, according

to the researches of Pfeiffer, the halteridium is not transmit-
ted from bird, by means of infected blood, whereas the
proteosoma is thus conveyed with great facility. The
apparent contradiction may thus be explained.

(3) The question as to the passage of the malarial
germs through the placenta has often been discussed, many
authors affirming that such does actually occur, although
there has never yet been reported any wells-tudied cases
which demonstrate, in a way to silence all objections, the
possibility of the infection of a fœtus in the mother's womb.
Most investigators, although having at their disposal a great
amount of material for study, have never seen a child with
malarial fever immediately after birth, nor have they
succeeded in finding the parasite in a fœtus removed from
the uterus of a woman who died of pernicious fever in whose
blood was an enormous number of germs, or in one born as
a result of abortion occurring shortly before the mother's
death. Numerous examples of this are to be found in the
literature; and the same, while naturally they do not
exclude the possibility of the passage of malarial parasite
through the placenta, demonstrate, nevertheless, that even
if such a thing as a congenital malarial infection exists, it
is at least exceedingly rare and exceptional In order to
explain this absence of malarial parasite in the blood of the
fœtus, which is certainly the rule, the fact has been invoked
that the malarial parasite shows no tendency to wander out
of the blood-vessels. Even in the case of small capillary
hæmorrhages, which are sometimes very numerous in the
brain in *comatose pernicious* fever, no parasites are found in
the extravasated red blood corpuscles, although they are
present in great numbers in the blood within the vessels in
the neighbourhood; the red corpuscles in the blood exudated
in malarial pneumonia also contain no parasites. All these
facts make it appear very improbable that the parasites
can pass from the maternal to the fœtal circulation during

their intraglobular existence. If it were held that this passage is possible during the brief period in which the very young parasites are living free in the blood plasma, in order to explain the negative result above-mentioned, we should have to assume that the fœtal blood is not adapted to the development of the parasites. The fact that the plasmodia do not invade the nucleated red corpuscles, and most probably not the young red globules, has been adduced in support of this theory. Some authors claim to have absolutely demonstrated the passage of the malarial germs from the mother to the fœtus Thus, Laveran cites two observations—one of Bouzian and the other of Bein—which, he asserts, prove beyond doubt the existence of congenital malaria. The original report of the first of these cases has not yet been published ; but Bein's case is not above criticism since the presence of malarial germs in the child's blood was noted too long after birth, and the possibility of *post-natal* infection could not be definitely excluded. Mannaberg cites, as positively conclusive, a case published by Ducheck in 1858. The case was one in which the mother of the child had suffered from intermittent fever during her pregnancy, and who died three hours after being born. At the autopsy there was found a notable enlargement of the liver and spleen, together with much black pigment in the form of irregular lumps and granules in the spleen and in the blood of the portal vein. There has been no publication of the original report of this curious case ; so that we may take it that no truly demonstrative case of congenital infection has been recorded in the literature since the discovery of the malarial parasites. Furthermore, the splenic enlargement may have been due to some non-malarial cause, *e.g.*, syphilis.

CHAPTER XIII.

PATHOLOGY OF ACUTE MALARIAL FEVER
AND MALARIAL CACHEXIA.

It is mainly by the study of cases of *pernicious* æstivo-autumnal fever that our knowledge of the anatomical alterations in the internal organs has been derived, for cases of regular intermittent fever are so rarely met with upon the *postmortem* table. The pathology of malarial fever has been vastly expanded by the discovery of the parasite of the disease by the observers already mentioned. One of the most interesting points, which at once strikes the careful observer, is the extreme distribution of the malarial parasite within the body, and the anatomical changes produced by them in each different case. The symptoms observed during life may be directly influenced by the localisation of the germs of the disease. The *melanosis*, which gives a characteristic colour to many of the organs, is the most striking point in the appearance of the viscera in cases of malarial fevers. The degree of their affection varies in different cases ; and the pigmentation in question is due to the accumulation of the pigment produced by the parasites from the hæmoglobin of the blood corpuscles. Its distribution, as in the case of the parasites, also admits of considerable variation.

Brain.—Cases of *comatose pernicious* fever furnish the most striking anatomical alterations in the brain. That organ may be the seat of few microscopical changes. Melanosis may be entirely absent. At times, however, there may be a slight *subpial œdema* with hyperæmia of the cerebral substance, and perhaps punctate hæmorrhages ; more commonly the gray cortex shows a gray or slaty or chocolate colour, which may be quite deep The vessels are markedly injected, and in places, punctate hæmorrhages

may be found. In these instances the microscopical changes
are most remarkable. The cerebral cappillaries are crowded
with parasites, which are, for the most part, within red
corpuscles, and may form an actual complete injection of
many of the cerebral vessels. This is generally most
striking in the grey substance. These parasites, usually of
the æstivo-autumnal type, may be in all stages of develop-
ment, though generally one of the stages is most marked.
Sometimes, in cases where death has occurred during the
paroxysms, actual thrombi of segmenting organisms may
exist Sometimes the organisms may not be so numerous,
but evidence of their previous existence is found in free
clumps of pigments and swollen pigmented endothelial cells,
as well as leucocytes containing pigments and red blood
corpuscles. There is usually decided granular and fatty
degeneration, and often pigmentation of the endothelium of
the vessels—a change upon which the punctate hæmorrhages
probably depend. Some endothelial cells may have greatly
swollen, almost occluding the lumen of the vessels : these,
as has been demonstrated, specially by Monti, may contain
a considerable number of well preserved parasites in various
stages of development; they may be shrunken within or
brassy corpuscles, or full-grown and free Occasionally
large *macrophages* are seen almost occluding the capillary;
these are, in the opinion of Monti, endothelial cells which
have broken up and circulate free in the blood stream.
These anatomical alterations are best seen in the *comatose*
form of the pernicious malaria. In some instance different
parts of the central nervous system may be differently affected.
In one case, for instance, studied by Marchiafava (Lav. Del.
III., Congr. del. Soc ; Ital. di Med. Int., Roma, 1890, 142),
where the patient died of symptoms of bulbar paralysis, a
special localisation of the changes was noted in the medulla.
In other instances the cerebral lesion may be slight; one is
unable to discover the collections of parasite in the capillaries,

as well as the degenerative changes in the endothelium thereof. There have been interesting results derived by Monti (Bull. d. Soc. Med. Chir. Di. Pavia, 1895) during the course of his researches regarding the nerve-cells in the grey cortex in pernicious malaria, using Golgi's method. In some cases the elements were, so far as could be made out, quite normal, while in others interesting changes were noted : these cases were chiefly those showing grave nervous symptoms, such as *coma* during life. Usually cells more or less profoundly altered were found, among other cells and fibres which were quite normal, although a tendency to a focal arrangement of these changes could be made out. The alterations affected chiefly the protoplasmic prolongations of the nervous cells of the cerebral cortex. Sometimes the prolongations appeared thinned and stuffed with fine nodes. Not infrequently these alterations were limited to the more delicate and distant branches, though it was not difficult to find cells of which all the *dentrites* presented the beaded appearance which is so well presented by the nerve-cells of animals died of inanition. In other points the alterations consisted of simple irregularities of contour in *dentrites* which were much thinned, extending from cells the bodies of which were sometimes normal, more often swollen, rarely thinned, shrunken, or atrophic. Coarser alterations were not wanting. Cells were found whose dentrites showed coarse varicosities and very marked constrictions, so that they appeared as if formed of protoplasmic matter connected only by the finest filaments of protoplasm. In the case of animals whose brains were made the seat of embolism by the injection of lycopodium, similar changes were observed. The axis cylinders were, in most of Monti's cases, well preserved ; the principal lesion appeared to consist in alterations of the protoplasmic prolongations. In some cases, specially in one severe case of comatose pernicious fever, certain alterations were made out in the *axones*. In this case the alterations in the nervous

elements appeared more marked throughout the brain than in other cases; the alterations in the dentrites were more frequent and marked, while the nervous prolongations also had, in many points, lost their normal character. Our author believes that these changes are due to the grave circulatory disturbance, many of these alterations are not dissimilar to those described in animals after the injection of ricin by Berkley, the occlusion of capillaries, lesions of their walls, the stasis, and the hæmorrhages produced by the malarial parasites

Spleen.—The changes in this organ in malarial cases are very characteristic. It is always enlarged; and what has been termed the acute *splenic tumour*, is pronounced. The capsule is tense. The parenchyma is cyanotic, and sometimes of a markedly slaty grey colour; it is soft and is often diffluent. In acute malaria death may often occur from rupture of an enlarged spleen. Microscopically, the pulp contains numerous number of red corpuscles, many of which contain parasites. These parasites may be in different stages of development. Generally the pigmented and segmenting forms may be found in large numbers; and sometimes, in the same organ, different areas show separate groups of parasites in different stages of development. Free forms of parasites are relatively rare One of the most striking appearances in the splenic pulp is, the presence of great numbers of *phagocytes*, some smaller and apparently leucocytic in nature, others resembling very large cells, rich in protoplasm, containing a single large nucleus and occasionally a coarse granulation. These cells may reach an enormous size. They are laden with pigment, either in large clumps or spheres, in rodlets, or in very fine granules; the granules sometimes present the same arrangement which they had in the body of the parasite. The fine pigment may be distributed in delicate lines throughout the whole mass of protoplasm of the phagocyte; it often seems to vary in colour

in different parts of the cells ; but, on focussing, this appear-
ance is found to be due to differences in plane.   These
large cells also contain red corpuscles, which are often
partially or completely decolourised and contain parasites ;
and, finally, entire small phagocytes with their included pig-
ments or corpuscles, as well as clumps of hæmoglobin, of
the colour of old brass, and fragments of degenerated red
corpuscles.   Golgi and Monti have called particular atten-
tion to the frequency with which these *macrophages* contain
apparently well preserved parasites in different stages of
development.   They believe that the shrunken and brassy
parasitiferous red corpuscles are engulfed in the phagocytes
as would be any foreign body, while the included parasites
continue their development within.   Some of the macro-
phages may show evidences of necrosis.   In some cases one
may find in the pulp actual focal necrosis, very much like
those seen in enteric fever.   In the intercellular spaces in
the pulp one may find free malarial pigment.   Pigmented
polymorphonuclear cells are relatively rare ; the small *mono-
nuclear* elements and the *lymphocytes* of the follicles never
contain pigments.   The capillaries are usually filled with
corpuscles containing parasites, while the splenic veins,
though they always contain fragments of blood corpuscles
and phagocytes containing pigments, show relatively few.

Liver. —The enormous number of parasites and the
vast amount of pigments contained in its capillaries give to
the liver very often an intense slaty grey colour.   The dis-
tribution of the pigment is different in this acute malarial
infection from that characteristic of repeated attacks.   There
is always a marked cloudy swelling.   Microscopically, the
capillaries are often clouded with *leucocytes* and contain
numerous *phagocytes,* some of the largest *macrophages* are
here observed, not infrequently the endothelial cells may
also be observed to show evidences of *phagocytic* action.
The perivascular tissue in the portal spaces may show numer-

ous pigments bearing cells; while frequently liver cells may be found to contain clumps of pigments derived from the blood and altered red corpuscles. This condition, similar to that observed in pernicious anæmia, accounts doubtless for the *polycholia* and the *subicteric* hue so commonly observed in the malarial fevers. In the intralobular veins, *macrophages* are not infrequently observed; ordinarily, relatively few parasites within red corpuscles are found within the vessels; these are numerous in the interlobular branches of the Vena Portæ. Amongst the hepatic changes that are of great interest, are occasionally occurring disseminated areas of local necrosis of the liver elements with fragmentation of the nuclei, wandering in of the leucocytes, and sometimes with evidences of proliferation of cells in the surrounding tissues. These changes are very similar to those already noted in typhoid and other acute infectious diseases, and proved by Welch and Flexner (John Hopkin's Hospital Bull. No. 20, March, 1892) to be produced in diphtheria, and by Read (John Hopkins' Hospital Reps., Vol. V, 1895) in typhoid fever, by a circulating toxic substance. The occurrence of these foci in the liver was first described by Guarneri (Atti de la R. Acad Med. di Roma, 1887, S. 2 v., iii., 247—266), who ascribed them to the cutting off of the nutrition by the extensive blocking of the intralobular capillaries with pigment bearing *phagocytes*. In association with many of these areas Baker (John Hopkin's Hospital Reaps., Vol. V., 1895) describes and pictures capillary thromboses.

Lungs. —The substance of the lung may show evidence of necrosis; and the alveolar capillaries present as a rule large numbers of *phagocytes,* which are smaller than the largest *macrophages* of the liver and spleen Occasionally, pigments may be found in the endothelial cells of the capillaries and small veins, but much more rarely than in the capillaries of the brain and of the liver. Leucocytes containing malarial pigments are seldom found in the interior of

the alveoli. *Mononuclear phagocytes* are much more frequent than ordinary *polymorphonuclear leucocytes,* which, when present, contain usually finer, smaller particles of pigments. The *macrophages* are generally collected about the periphery of the smaller veins. The endoglobular parasites usually show all stages of development. The endothelium of the capillaries and small veins rarely contains pigments, in sharp contrast to the condition existing in the brain. It is a remarkable fact that the areas of broncho-pneumonia which are not infrequently found, contain only the ordinary polymorphonuclear leucocytes and alveolar epithelial cells, pigmented elements being very rarely present. The capillaries of the septa may be filled with pigments and macrophages. The diminished vitality of the pigment-bearing cells, which have, to a certain extent, lost their motile power, and are thus less able to pass through the vessels, is considered by Bignami to account for this.

Kidneys.—The gross appearance of these organs differs but little from the normal, and the changes in them in acute malaria are usually much less marked than in the liver and spleen. Evidences of pigmentations are usually wanting on gross examination. The malarial parasites and phagocytes are usually present in smaller numbers, the quantity being disproportionately small in comparison to the alterations of the parenchyma which are sometimes to be found. The glomeruli are ordinarily and considerably pigmented, the pigment at times being seen within large white cells inside the vessels, sometimes in the endothelium of glomeruli. Endoglobular parasites are rarely seen in the capillaries of the glomeruli; they are more common in the intertubular vessels, but are rare even there. Focal necrosis of the epithelium, specially of the convoluted tubules, are at times some of the marked changes in the parenchyma. The most important lesion consists in exfoliation and degeneration of the epithelium lining the capsule. Albuminous exudates within the

glomeruli were found by Bignami only in *algid pernicious* fever. Pellarin (Arch. de Med. nav., 1865), Benoit (*ibid*), Kièner and Kelsch (Arch. de Phys., 1882) have well described the renal changes in cases of hæmoglobinuric fever. The capsule of the gland is easily detached; its consistency is normal. The kidneys are somewhat increased in size, the colour varying from a deep reddish-brown to a light yellowish-brown coffee colour in more anæmic individuals. When the colour is pale, irregular pinhead points and blotches of a maroon colour are to be seen upon the surface, some as large as several millimetres in diameter or area. They are also scattered throughout the cortex. These have been described by Kelsch and Kièner to be due to pigment deposits; they are not visible in more congested kidney. The pyramids are of a deep-red colour from the intratubular hæmorrhages. There are also peculiar changes to be seen under the microscope. The epithelium of the convoluted tubules and of the large branches of Henle's loops, are very opaque, the nuclei being scarcely visible. This is due to an infiltration of the protoplasm with a diffuse colouring matter, and fine pigment granules which are rendered more evident by caustic potash. These granules are extremely small, and separately appear of a yellowish-colour, while, *en masse*, they have a brown shade. The epithelial cells are swollen, and bulge into the lumen of the canal. Occasionally a cell shows a hyaline protrusion, which seems on the point of escaping. In some tubes the epithelial covering is represented only by a thin protoplasmic layer with a homogeneous surface, appearing as if eroded down to the level of the nuclei. The lumen of the tubule is filled with clumps of amorphous material or *casts* mixed with this pigment to a greater or less extent. The brown specks and blotches are seen microscopically representing groups of tubules, the epithelium and lumen of which are crowded with similar masses of pigment ; but pigment may also be found in

larger granules—granules nearly as large as the red blood corpuscles, and more or less spherical; they are refractive, of a colour varying from a yellow to a deep brown, and are sometimes accumulated in epithelial cells which bulge so as almost to occlude the lumen. Sometimes they occupy the lumen and form conglomerations. Taking the form and shape of casts, they are sometimes fused into a vitreoid mass. Between the opaque dark casts formed by the fine brown granulations and the almost vitreoid casts composed of the large orange-coloured granulations, every intermediate stage may be seen in the same preparation. Generally, this pigment gives no reaction for iron, though Kelsch and Kièner have obtained this reaction from certain granules in one case. The finely granular substance is found, according to these authors, more particularly in cases where death has occurred in a pernicious paroxysm, while the larger forms of pigment are more frequent in cases of long duration. In the glomeruli, as well as in the blood, Kelsch and Kiéner have never seen the large varieties of the granules though the finer granules are numerous. Between the glomerulus and the capsule, usually near the mouth of the tubules, there is often quite a collection of granules, which are also found sometimes in epithelial cells, sometimes free. In the glomerulus itself one may see fine granulations disseminated in its substance, and apparently included in the cells of the capillary walls. More rarely granulations may be accumulated in a capillary loop. In some cases there are small interstitial hæmorrhages. The pyramids show few changes. The same varieties of casts as above noted may be found, and the same collections of pigments. The epithelium is usually intact, though sometimes protruding and vesicular cells suggest that they may take part in the formation of hyaline material. Blood-corpuscles are almost invariably found to fill a number of the renal tubes.

Suprarenal capsules.—Pronounced alterations may be

found in connection with the *adrenal glands.* There are irregular areas of vascular dilatations, parasites being numerous in the distended vessels. Macrophages, with varying contents, may be present in considerable numbers. True adrenal cells may be found enclosing malarial pigment and infected corpuscles, and the endothelial cells of the vessels may be phagocytic.

Gastro-intestinal canal.—Beyond the presence of melanosis, there are few changes to be seen in the stomach and intestines under ordinary circumstances. It is to be remembered that the intestinal mucous membranes may be of a dark steel-gray colour in conditions other than malaria. In the majority of cases the gastro-intestinal mucous membrane is not particularly sought by the parasites, though the microscope may reveal a considerable number of them, specially of the full-grown and segmenting parasites, in the capillaries of the mucous membrane, together with numerous pigmented cells and apparently few pigment clumps. This region may be the seat of the main localisation of the affection in other instances, as pointed out by Marchiafava and Bignami. Cases of this sort are frequently associated with gastro-intestinal symptoms, some showing a clinical picture very similar to that of Asiatic cholera. Microscopically there may be intense hyperæmia with *punctate hæmorrhages* in the gastro-intestinal mucosa ; and there may be a distinct dusky slaty tinge as well. Here the capillaries throughout the gastro-intestinal tract may be crowded and blocked with parasites, free and contained in the red corpuscles, or in phagocytes. As in the case of the brain, actual thrombosis may exist with necrosis of the epithelial covering and ulceration

Bone-marrow.—Though often almost black, the bone-marrow is generally of a dark slaty colour. The small vessels are filled with endoglobular pigmented parasites, while numerous macrophages, containing pigment and red

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blood-corpuscles, may be found about the periphery of the lumina of the vessels. At times, between the corpuscles, Bignami (Atti d R. Acc. Med. Roma, Ann XVI, v; 1890) found numerous ovoid bodies which, from their size and staining propensities, he believed to be free spores. Free pigment clumps are apparently to be made out at times. Not only in the vessel, but also outside of these, the parasites are to be found in greater or less number. The macrophages are specially numerous, even in the pulp.

There is little that can be considered as characteristic in other organs. The above description applies to the anatomical alterations observed in cases of acute malarial infection   We shall now consider chronic malarial *cachexia, i.e ,* the changes following repeated or chronic infection with the disease.

MALARIAL CACHEXIA.

The changes just described have to do with acutely fatal cases of malaria ; and important pathological changes may occur in various organs and tissues, *e.g ,* the *blood, spleen, liver, bone-marrow,* and *heart,* as the result of long-continued or frequently repeated attacks. Now we should consider each organ separately, as follow :—

Spleen in Malarial cachexia.— In malaria enlargement of the spleen is both constant and considerable. It may be of enormous size reaching beyond the umbilicus and as low as the pubes. It is firm and hard, and its border is sharp. The capsule is usually much thickened, and white fibrous cartilaginoid plates occur upon the surface. On section, the *trabeculæ* are very prominent, and the organ has often a somewhat slaty colour. The acute splenic tumour is caused chiefly by the aggregation in the pulp of the spleen of an enormous number of red corpuscles, which have become either shrunken and brassy-coloured or deco_ lourised, and are found included in the colourless elements of the spleen as brassy-coloured fragments or hyaline masses ; by the continuous aggregations of colourless

elements containing pigment, red corpuscles, or parasites, which collect from all parts of the body, and many of which are necrotic ; and, thirdly, by great numbers of red corpuscles, containing parasites, some of which apparently pass through the vessel walls by *diapedesis*, and seek the columns of the pulp, where they are for the most part enclosed by the epitheloid elements. While, as a result of this proceeding, a considerable number of the proper elements of the spleen become necrotic, others, as well as the pulp in the follicles, undergo *karyokinetic* division, while all these are followed by a marked hyperæmia and acute tumour of the splenic pulp. Thus the spleen is converted into a place for the deposit of *débris*, while processes of regeneration have begun to appear at the same time during the same infection. The tissues in the neighbourhood of these collections of necrotic elements or those surrounding the necrotic areas of the splenic pulp. when the actual infection is at an end, and the acute hyperæmia of the spleen has ceased, show certain changes which, on the one hand, tend to produce permanent alterations, and on the other to lead to a partial reparation of the parts. In those parts where a considerable portion of the splenic tissue becomes necrotic, or disappears, being carried away by the lymphatics, the splenic vessels become considerably dilated, forming a net-work of *venous lacunæ* which are separated by thin layers of pulp. This results in a tissue resembling that of an angioma. In those cases where a more marked destruction of the splenic tissues has occurred, and where every trace of the pulp is gone, parts become represented by extensive areas of tissue which consists of wide *cavernous sinuses*, the *septa* of which are composed of a very delicate connective tissue, rich in giant cells, similar to that of the bone-marrow. Some of the follicles become necrotic and fibrous. While this occurs a process of regeneration yet more extensive takes place, starting for the most part from the follicles, but also some-

times from the splenic pulp. The follicles become hyper-
plastic, reaching sometimes three or four times their normal
size. This new form of lymphoid tissue, starting from
the follicles, may be seen sometimes to surround necrotic
areas of splenic tissue which become smaller and smaller
and finally disappear. In the neighbourhood of these
hyperplastic follicles occurs a hyperplasia of the true ele-
ments of the pulp, while the reticulum becomes thickened
so as to give rise, in preparations, to very beautiful and
clear figures, such as are not to be seen in the normal spleen.
The pigment, and probably the greater part of the necrotic
elements, are carried on toward, and collected about, the
periphery of the follicles, so that the diffused melanosis of
the pulp is followed by a perifollicular melanosis. The
pigment then passes on into the lymphatic vessels of the
sheath of the arteries, and of the connective tissues of the
septa. This results, on the one hand, in thickening of the
vascular sheaths and of the septa ; and, on the other hand,
in the appearance—giving sometimes the picture of a
lymphangioma and resulting in chronic lymphatic stasis—
of single or multiple cysts. It is easy to understand the
gradual development of the enormous splenic tumours,—in
which, sometimes, it is difficult to recognise the original
structure of the organ, even under the microscope—when
we consider that, after each new infection, fresh processes
similar to these must occur.

Liver in malarial cachexia.—In the same manner
the anatomical alterations occurring in the liver in chronic
malaria may be traced from those occurring in the acute
infection. In the acute infection an enormous number of
phagocytes, pigmentiferous or *globuliferous*, coming in great
part from the spleen, invades the capillary network of the
liver, while the parasites are generally scanty. The cir-
culation is slowed, the capillary network becomes dilated,
while a certain amount of the pigment is taken up by the

endothelial cells of the vessels, and later by Kupffer's cells. The pigmented endothelium becomes swollen and in part necrotic. These vascular changes are followed by new areas of blood stasis. At the same time, as has been noted, many of the liver cells suffer alterations, either undergoing an acute atrophy from pressure, or a coagulative necrosis. These areas are sometimes quite extensive. In other instances many cells are found to be filled with blocks of yellowish iron containing pigment, resulting from the early death of many red corpuscles. At the same time a certain number of hepatic cells, Kupffer's cells, and endothelial cells multiply by *karyokinesis*. Polycholia, an increase in functional activity, and acute hepatic tumour result from all this. But there is an escape of a small part of the great number of pigmented elements which enter the liver, passing through the branches of the suprahepatic veins. The greater part is taken up by endothelial and perivascular cells, so that the melanæmia is followed by a melanosis of the vessels. The pigment then passes forward out of the capillary network into the perivascular lymph channels, there it is collected in large blocks enclosed in white cells. These carry the pigments following the lymph channels to the periphery of the lobules, and perilobular melanosis follows thus to the interlobular melanosis. Masses of the pigment are to be found, three or four months after the end of the infection, in large blocks, for the most part endocellular, in the perivascular lymphatic tissue of Glisson's capsule; and all this results from the extension of the process. There occur, on the one hand, permanent alterations, and, on the other hand, regenerative processes, while this migration of the pigment is going on. Where the dilatation of the lymph and blood vessels and the degeneration and pigmentaton of the vascular elements is most marked and extensive, no regeneration may follow the atrophy and necrosis of the endothelial and liver cells.

The dilatation of the vessels increases and becomes per-
manent. The greater part of the remaining liver element
disappear ; only a few remain in an atrophic condition, the
tissue showing an angioma like appearance consisting of vas-
cular network, but which may be recognised a stroma consist-
ing of Kupffer's cells. Small lymphatic cysts may occur
where the dilatation of the lymph vessel is most marked. An
active regeneration of the tissue elements occurs about the
atrophic or necrotic hepatic cells, in all parts of the liver,
when the normal blood current has been restored after the
disappearance of the pigment, and the necrotic masses in
general, form the endothelial cells of the vessel walls. The
young hepatic cells become arranged with great regularity in
long rows on both sides of the old elements. Thus, when the
stroma remains intact, an interlobular regeneration may occur.
These regenerative processes are accompanied by the appear-
ance of giant cells with budding nuclei, such as are found
in the embryonic liver. In parts of the liver that have not
been freed from the collections of pigments and parasites, the
regeneration never makes its appearance   A hyperplasia
of the perilobular tissue follows the migration and collec-
tion of the pigment in this tissue, so that the surroundings
of the lobules are more distinct. These degenerative and
regenerative changes result, then in a marked increase in
the size of some lobules and a diminution in size and
atrophy of others. As this process accompanies each
acute infection, one can naturally understand the chronic
perilobular, monolobular hepatitis of malaria, which is
characterised by the presence of zones of hyperplasia or of
atrophy of parenchyma, by chronic blood and lymph stasis,
by the formation of areas of angiomatoid tissue, *lymphec-
tasis*, and *lymphatic cysts*. The large hepatic tumour, which
is so well known, with smooth surfaces and lobules of irregular
size, originates in this manner. The changes in the liver
may be described in five stages :—

(1) The organ appears congested, while the lobules are not sharply distinguishable and show in severe cases a decreased melanosis. The microscopical characters are about the same as those of the liver in acute malarial infec_ tions. Microscopically, at this period, a little after the termination of the acute infection, it may be noted that the parasites have disappeared from the capillaries of the liver, the pigmented endovascular macrophages have in great part gone, and the pigment is entirely collected in the endothelium and in Kupffer's cells. These parts of the hepatic lobules in which necrosis or degeneration has occurred, undergo a marked atrophy, the necrotic and degenerative elements are carried away in the phagocytes, while there occurs a dilation of the network of blood-vessels

(2) On gross examination in a more advanced stage, the lobules are distinct. The melanosis continues to diffuse throughout the lobules, but is more marked at the periphery. The organ is still congested. The particular features of this stage are that, on the one hand, the hepatic lobule frees itself from the accumulation of pigment and the necrotic remains, which become collected towards the periphery of the lobule, while, on the other hand, an active process begins by means of which a partial regeneration of the parenchyma tends to take place.

(3) The diffuse melanosis of the lobule, with the greater prevalence of pigment towards the periphery, is in this stage succeeded by an exclusively perilobular melanosis. The liver is enlarged, the consistency somewhat increased, and the surface smooth. On section, one may see that all the lobules are surrounded by a slate-coloured line, in the neighbourhood of which the colourisation of that part of the lobule is somewhat brown. In general, the slaty lines marking out each lobule form an exquisite network. The size of the individual lobules varies greatly ; some are two or three times the normal size, others are markedly diminished.

Microscopically, it may be observed that the degenerative alterations of some lobules have led to the formation of false angiomata, and of lacunæ are cysts of lymphatic nature. Other lobules, by the process of regeneration already described, have increased notably, in volume. The pigment has become extravascular; the white *mononuclear* and *polymorphonuclear* cells have affected its transportation through the capillaries and perilobular lymphatics.

(4) The pigmentation is greatly diminished, and scarcely visible to the naked eye, in cases in which the acute infection has passed for three or more months. The liver is notably enlarged and congested. The surface is smooth On section, one may see the lobules distinctly marked, surrounded by a most delicate reddish-brown border; the consistency is somewhat increased. The melanosis will be seen to have become exclusively perivascular, if the microscope be employed.

(5) One arrives, lastly, at the definite terminal form of the chronic malarial hepatic tumour. The microscopical characters are the following: The liver is increased in size and weight, sometimes enormously; the surface is smooth, the capsule is a little thickened. On section, the appearance is finally granular, the lobules are distinct, a little prominent, and surrounded by a zone of slightly pinkish tissue. Microscopical examination shows the disappearance of all malarial pigment. The alterations of the parenchyma are similar to those described in the last two stages. The lobules of varying size are surrounded by a hyperplastic perilobular connective tissue. The connective tissue of the larger septa is, on the other hand, of about normal volume. A notable dilatation of the capillaries, with stasis of the colourless corpuscles, persists. The hepatic cells are altered in form in the zones where the dilatation is most marked. There is considerable difference in individual cases in the extent of these various lesions. There are cases, for example, in

which, despite the enormous increase in the weight of the organ, there may be no very marked dilatation of the capillaries, nor are false angiomata or lymphatic cysts to be found; while, on the other hand, the hyperplasia of the perilobular connective tissue, and the increase in volume of many lobules, may be more marked; there may be an evident hyperplasia of the parenchyma—evidenced by hepatic cells with many nuclei, and nucleili rich in chromatin substance. In other cases, on the other hand, one of the chief factors in the enlargement of the liver may be the enormous development of the cysts and false angiomata.

Bone-marrow in malaria cachexia.—The marrow of the long bones, for example, of the femur in the upper and lower fourths, is usually red, and of a consistency greater than is generally seen in acute infections, in the case of individuals who have had numerous relapses of malarial fevers. The microscopical alterations are various; generally the signs of an active proliferation of the proper elements of the marrow are present. This leads to an increase in the *hæmatopoïetic* activity. There are factors, such as the degenerative and destructive alterations which take place in the bone-marrow during acute infections, which injure, to a varying extent, and through a varying length of time, the hæmatopoietic functions of the marrow. There may be cases in which the new formation of the *hæmatoblastic* marrow is wanting or entirely insufficient. The post-malarial anæmia is necessarily progressive in these cases. Lastly, in other cases, very rare indeed, the bone-marrow presents the microscopical features which exist in acute pernicious anæmia, particularly the presence of a considerable number of *megaloblasts*.

Blood in malarial cachexia.—The changes in the blood in malarial fever are of great importance. They have been arranged in two *categories*, the first being due to the direct action of acute malarial infection, and involving both

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red and white corpuscles (pigmented globuliferous parasite-
infected leucocytes), the other being secondary to the anæmic
condition which is the result of the parasitic invasion. Among
the first, the most important are the lesions of the red
corpuscles caused by the action of the parasites, which develop
within them and which are nourished at their expense Some
of these lesions differ according to the kind of malarial
parasites, the gravest being found in the *æstivo-autumnal*
fevers. But melanæmia is common to all forms of malaria
and constant in that affection. In the tertian form specially,
swelling of the red corpuscles is to be observed. The red
cells are invaded by the parasites, and gradually increase
in size until they are two, three, or even more times the
usual size ; at the same time they gradually lose their con-
tour until they finally become pale, so much so that some-
times the corpuscles containing adult parasites, specially
the forms known as *gametes*, are scarcely to be recognised
by their outlines. They frequently are changed in shape,
becoming more or less oval. Corpuscles which have lost
their hæmoglobin are seen, in fixed and stained preparations,
to contain really the adult parasites which seem to be
free in the plasma. The so-called brassy bodies described
by Marchiafava and Celli (found in the æstivo-autumnal
fevers, and only occasionally, as Bastianelli and Bignami
have noted, in the ordinary tertian) best exemplify the
shrinkage of the corpuscles with changes in the colour of
the hæmoglobin. The lesion may be designated as *ery-
thropycnosis*, for the red corpuscle takes on the colour
of old gold or of brass, becomes smaller, and shrivels.
Various conditions give the brassy bodies. They are
specially to be met with in the *apyrexia* preceding a fresh
febrile attack, when all, or nearly all, the *æstivo-autumnal*
parasites in the circulating blood have become pigmented
at the periphery, or have pigment in the centre, or a little
eccentrically. They may also be found after the adminis-

tration of quinine, in which case many of the red corpuscles containing young, non-pigmented parasites are also brassy. In this latter event, we must believe that quinine in its final action determines a necrosis, not only of the parasites but of the red corpuscles containing it ; and, in fact, after the lapse of time all these bodies disappear from the blood. Quinine does not cause these changes in all parasite-infected corpuscles, for it not rarely happens that after its administration many free parasites are found in the blood, evidently having come out of the red blood-corpuscles. What becomes of the parasites contained in the brassy bodies, that is to say, previous to a febrile attack, independently of the action of quinine, is far more difficult to determine It being known that all, or nearly all, the parasitic forms which reach the stage of multiplication are found stationary in the viscera, it is a reasonable certainty that the adult forms circulating within brassy bodies die with the corpuscles containing them : in other words, it seems probable that the necrosis of the corpuscle prevents the further development of the parasites. Followed, in all probability, by the death of the included parasite, it is likely that the *erythropycnosis* represents a necrosis of the red blood-corpuscles ; for we sometimes see parasites which have completed fission within brassy bodies, though in such a case it is probable that the corpuscle has not long been brassy, but that the alterations in its conditions occurred after the complete development of the parasite. In the *æstival* fevers, partial decolourisation of the red blood corpuscles is not infrequently encountered. In some red globules containing bodies with blocks of pigments, we find the hæmoglobin collected and, as it were, condensed around the parasites as though attracted to it ; while the remainder of the corpuscles is seen to be more or less decolourised and usually shrivelled and wrinked. In the crescent bodies, which are surrounded by a thin layer of hæmoglobin forming a sort of membrane round them, the rest of the

corpuscles being recognisable only by its very faint outlines, this same condition of things is often to be found. The hæmoglobin may be seen in some cases, in which two bodies with central pigment masses are included within the same blood-corpuscles, to form a certain kind of halo around each one, the globule being perceptible only by the delicate line at the periphery. This would lead us to believe that at the periphery of the corpuscles there is a stratum of tissue differentiated from, and more resistant than, the discoplasm, and forming a sort of membrane. In some cases, indeed, the parasite appears to be confined within a sort of bag, which is not well filled, and whose walls are withered and wrinkled. When an adult parasite comes out from a corpuscle, or a fission form is set free, and the spores disperse, this peripheral stratum appears to burst ; at the same moment the hæmoglobin is lost in the plasma. The fact that the pseudopodia—even the large pigmented pseudopodia of the tertian parasite—do not project beyond the surface of the red corpuscles may be due to the presence of this resistant peripheral layer. It is by no means infrequent to observe fragmentation of the parasite-infected corpuscles. Some- times one sees a corpuscle containing, for instance, a pigmented æstival body, divided into two parts, forming two little corpuscles, in one of which the parasite —*parasiteferous schistocytes*—is contained. As explaining the stagnation of the corpuscles in certain vascular areas, great importance has been attributed to the changes in the physical properties of the parasite-infected corpuscles. A tendency to agglutination on the part of the red corpuscles which were not infected with the parasites was observed by Bignami in only two cases of hæmoglobinuria. This author, when studying the dis_ tribution of the parasite in the vessels of the various viscera in pernicious fevers, noticed that the parasite-infected red corpuscles, in the veins of certain calibre, showed a tendency to place themselves against the walls of the vessel, and

that sometimes they would gather in one vein, being grouped together as if agglutinated. This circumstance he endeavoured to explain by assuming a diminished elasticity in the *discoplasm*, and qualitative alteration in the surface which had apparently become viscous. Red corpuscles containing æstivo-autumnal parasites, specially when these are adult bodies, are less adapted than normal ones to the circulation on account of this fact. This has been proved by actual research. If an ordinary fresh preparation of æstivo-autumnal blood, in which are numerous corpuscles containing bodies with blocks of pigment, we cause a current by pressure, we shall see that the corpuscles containing the above-mentioned bodies scarcely move, and appear almost to cling to the glass. Less elasticity and a greater viscidity than normal may therefore be presumed for many of the corpuscles, even those which present no alterations recognisable under the microscope. In malarial cases, by far the most characteristic alteration in the blood is *melanæmia;* which same, at least so far as we are aware, occurs only in this disease and is *pathognomonic* of it. It consists of the presence of a pigment in the blood, the determination of which is easy if a thin layer of blood be subjected to microscopical examination—of a brownish or black or brownish-yellow or reddish-brown colour, which occurs in the form of granules, rods, needles, or blocks, the joining together of which gives conglomeration of greater or less size. In rare cases they are free ; but, as a rule, they are included within the body of the malarial parasite or in the leucocyte. In former times it was thought that this pigment was derived from the colouring matter of the red blood-corpuscles, and many were the opinions held thereon. As early as the century before last, some physicians observed that various organs were of a black or dark appearance in grave malarial fevers. Particles of black pigments were first observed in the blood by Meckel, who said that they came from the spleen. The term " black

spleen" was invented by Tigri to describe the melanosis in connection therewith. The hypothesis that the pigment originated in the spleen was advanced by Virchow, who noticed numerous pigmented cells in the blood of a man who had died with dropsy after many attacks of intermittent fever. To him and Frerichs we owe the theory that *melanæmia* represents *dyscrasia* due to the alteration of some organ. To the latter observer we owe an accurate description of melanæmia, and of its effects upon the organism. He observed in the blood free black granules and molecules and pigmented cells resembling leucocytes, now fusiform and now cylindrical in shape ; accumulation of black granules held together by a pale substance, or having an involucrum of hyaline substance which was sometimes thick and sometimes thin, were also described by him. Frerichs believed that the pigment was formed in the spleen, because, firstly pigment is found in the normal spleen ; secondly in a melanæmia there is always more pigment in the spleen than in the general circulation ; and, thirdly, in the general circulation we find pigmented splenic cells. He held, moreover, that sometimes even the liver might participate in the formation of pigment. He agrees with Virchow that in intermittent fevers the pigment enters the circulation after its formation in the spleen. As to the method of its formation, Frerichs thought that in malarial hyperæmia of the spleen the blood was poured in large amount into the *lacunæ* of this organ, stagnated there and was there destroyed, whence the formation of masses of pigment from the hæmoglobin of the red corpuscles That this formation of pigment does not occur in hyperæmia of the spleen from other causes is because chemical changes of the splenic juice are produced in malaria which menace the existence of the red blood corpuscles. Meigs lays stress upon the intimate connection existing between the formation of black pigment and intermittent and remittent fevers, stating that he has looked in

vain for the same condition in other diseases. He notes the marked diminution in the number of the red corpuscles during acute infections, and accurately describes the condition of the viscera in the cadaver, dwelling upon the characteristic aspect of the various nervous centres in which, as a rule, the pigment is found in minute granules within the capillaries, sometimes in such abundance as to modify the colour of the nervous tissue. He affirms that the pigment granules are found within cells not to be distinguished from leucocytes of splenic cells ; but sometimes the pigmented cells have an oblong or spindle-shaped outline. In the splenic pulp he claims to have found ied corpuscles in various stages, not only of disintegration, but of metamorphosis into true pigment ; so that he holds with Frerichs that it is from the hæmoglobin that the black pigment originates. The latter is most abundant in spleen and the portal vein, but in grave cases it is found in the whole organism. On the other hand, Colin insists that the formation of the pigment occurs not only in the vessels of the spleen, but also in those of other organs ; but he also asserts, without giving sufficient reasons for this belief, that this formation of pigment has nothing specific in its nature, because it occurs in other diseases as well; for instance, in the mesenterie glands in typhoid fever and dysentery. On account of the more rapid and more marked destruction of red corpuscles, he holds that in malarial infection, the condition is more conspicuous than in other diseases. The theory of the primary formation of the pigment in the spleen, advanced by Virchow and Frerichs, is supported by Moslar, who holds that the special structure of the spleen lends itself to the formation of the pigment, that is to say, that the blood flowing from the capillaries into the intermediate blood vessels not rarely stagnates there, so that conglomerations of red corpuscles occur which gradually becomes converted into pigment. In the enlarged spleen of malaria

he believes, with Frerichs, in the occurrence of a chemical change in the quality of the splenic juice.   In this particular, Arnstein's researches are important.

He Arnstein) maintains that the pigment is formed in the circulating blood during the febrile attack, and is deposited by it in the spleen, liver, and bone-marrow.   He observes that the pigment is found in the blood free or included in white corpuscles, which is the usual occurrence, during the fever or shortly after.   On examination of such organs as are most *melanotic*, the spleen, bone-marrow, and liver, he finds that they contain pigment not only in the blood-vessels but also around them, and only in cases of recent infection he does find it in other organs, such as the brain and the kidneys.   He holds that the theory of Virchow and Frerichs is not tenable but believes that the *melanæmia*, the presence of black pigment in the circulating blood is the primary occurrence, and the *melanosis* of the spleen and the liver the secondary: indeed, melanæmia may be found only for a short time after the febrile paroxysm, which would not be comprehensible of the melanosis of the spleen, if it were primary; furthermore, the deposition of the pigment in the circulating blood corresponds perfectly with what occurs when one introduces within the circulation such a colouring matter as *cinnabar*.   Therefore, during the febrile attack, the red corpuscles, according to him, are destroyed, and the pigment which is formed is rapidly taken in by the leucocytes which stagnate in the veins and capillaries of those organs in which the circulation is slowest, that is to say the spleen, the liver, and the bone-marrow, whence the pigment is deposited in the tissue of these organs.   As to the mode of formation of the pigment, he admits that he has no knowledge, not having been able to follow the process of disintegration of the red blood-corpuscles through all its stages.   He holds it to be probable that the pigment is formed in the blood serum from hæmoglobin which has

come out of the red blood-cells. He does not believe that the pigment is formed within the leucocytes, as Langhaus observed in hæmorrhages, because we find free pigment in the blood and no globuliferous cells. These are few in comparison to the enormous amount of pigment present in the circulating blood, and are found in the spleen and in the bone-marrow. These opinions have been upset by more recent investigations.

Kelsch, speaking of the melanæmia, describes in the blood of malarial patients, specially those suffering from pernicious fevers, the presence of free pigment, or pigment included in hyaline masses, or more often still in white corpuscles. He notes that there are *melaniferous* elements which contain pigment granules arranged in wreath form ; he describes others which give a brownish reflection in the marginal zone, and contain fine black granules ; and in the blood of the splenic and portal veins he found *melaniferous* cells which were most varied in form and size, being *spherical, polyhedral, ovoid, elongated, biscuit-shaped,* etc. As to the distribution of the pigments, from a study of the various organs in patients who had died of pernicious fever, Kelsch comes to the conclusion, that it behaves exactly in the same way as granular colouring matter injected into the circulation. In opposition to the theory of Virchow and Frerichs, he believes that it is formed in the circulating blood ; in fact, in a case of *fulminating* pernicious fever he found little pigment in the spleen, while the blood was filled with it. As to the mode of formation, he cannot admit that any of the elements represent the stroma of decolourised red cells with pigment granules formed at the expense of the hæmoglobin, because he did not succeed in finding the intermediate stage of this retrogressive metamorphosis ; nor does he admit Langhaus's theory of the intracellular formation of pigment, because the pigment is also found free in the blood. He takes refuge in the hypothesis which applies also to what occurs in the blood on the injection of cinnabar—that the melanotic

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material proceeding from the destruction of the red blood corpuscles exist in the serum in a state of solution, and when the blood becomes saturated is precipitated in the form of granules which are speedily taken in by the leucocytes.

As early as 1879, Marchiafava suspected that the pigment was formed within the red blood-cells, and subsequent researches have confirmed his conclusion about it. From his study of the splenic pulp, and of the bone-marrow in melanæmic children, he came to the conclusion that the red blood-corpuscles do not give rise to the formation of pigment after their disintegration ; but that, on the contrary, the conversion of hæmoglobin into *melanin* occurs by degrees within the corpuscles itself.

Afanassiew, having doubts as to the origin of the pigment from the red corpuscles, suggested the parasitic nature of the pigment granules and held them to be analogous to the *Micrococcus chromatogenus* of Cohn. The theory of melanæmia was definitely established by Laveran, Richard, and Marchiafava and Celli. The first-mentioned observer's researches, while they also led him to assert the parasitic nature of the pigmented bodies, nos. 1, 2, and 3, did not lead him to an exact recognition of the genesis of melanæmia. In fact, not having observed progressive endoglobular development of his pigmented bodies, he was inclined to believe, at the beginning of his researches, that the pigment was an integral part of the parasitic body : so much so, indeed, that in the waters of malarial regions he sought a pigmented parasite, but not finding it, he advanced the theory that a destruction of the red blood-corpuscle might give rise to the pigment.

It is probable that, in spite of all contradictory evidence, these long series of researches have proved (specially the observation of Arnstein and of Kelsch) that the black pigment is formed in the circulating blood, and that, consequently, the melanosis of such viscera as the liver and.

the spleen is secondary to the melanæmia ; but that the genesis of the pigment is still uncertain. It is obvious that, except by a methodical study of the alteration of the red cells preceding the formation of the black pigment no convincing solution of the question has been accomplished as to whether the pigment was formed in the serum from colouring matter which had escaped from the red corpuscles, as Arnstein believed, or whether the melanotic substance did exist in the plasma in a state of solution and become precipitated when the plasma was saturated ; and also if it was a part of the body of the parasites or was its formation from the red blood-corpuscles determined by the action of the parasites.

This subject was thoroughly investigated, in 1883, by Marchiafava and Celli, who came to the conclusion, reached by Marchiafava a few years previously, that it is within the red cells themselves by degrees that the conversion of hæmoglobin into melanin occurs, and that the red corpuscles do not give rise to the formation of pigment after their disintegration. The appearance within the cells of spherical or ring-shaped bodies, easily stained by some of the anilin dyes, *e.g.*, methylene blue, was seen by these authors to usher in the changes started by the red corpuscles and leading to *melanæmia.* In these little bodies, which, as the substance stainable by methylene blue increases, increase both in size and number, small granules of pigments begin to appear subsequent to this alteration. From all this, these authors were able to assert that the formation of pigment occurs within the red cells which have already undergone characteristic alterations, and this even before they had recognised the parasitic nature of the little bodies which could be stained by methylene blue, so that all previous theories became untenable.

The theory of *melanæmia* became cleared up on the establishment of the parasitic nature of the spherical and

annular bodies. It is intimately connected with the life-cycle of the parasite : so much so, indeed, that a description of the genesis of the melanin cannot be separated from that of the malarial germ itself. In the various vascular areas during an acute infection, the distribution of the grains and blocks of melanin corresponds in the same manner finally to the distribution of the parasites. This explains the fact that the distribution does not alto-gether correspond to that of inert powders injected into the blood, as Kelsch maintained, although, as a rule, it resembles it greatly. For instance, the melanosis of the brain in comatose pernicious fevers, and sometimes the enormous accumulation of pigmented parasites, in the intestinal capillaries in choleraic pernicious fevers, are facts which it would be impossible to understand, unless we bear in mind that we have to do, not with free circulating pigment granules, but with pigmented parasites. Therefore, the morbid anatomy of pernicious fevers furnishes the law of distribution of the black pigment. Regarding the successive changes which occur in the formation, by parasitic action within the red cells, or melanin from hæmoglobin during an acute infection, we have seen that when fission of mature parasites is fairly accomplished, a residuum of segmentation is left, formed chiefly of a lump of melanin or an accumulation of black granules. When disaggregation of the spores has occurred, the pigment becomes free in the plasma, and thence is quickly taken up by the leucocytes and in part by the endothelium, specially in certain organs. The latter process is well seen in the brain and in the liver. This process occurs with every species of malarial parasite. But it is not only from the multiplying bodies that the pigment found within the leucocytes and the endothelium is derived. In part it comes from the parasite-infected red corpuscles which die before the development of the parasite is complete, in part also from the pigmented

parasites that may escape from the red corpuscles and so become free in the plasma. The first occurs chiefly in æstivo-autumnal fevers, in which, as we have seen, many corpuscles, (red) become brassy ; both brassy corpuscles and included pigmented parasite may be taken up by a leucocyte. The second is somewhat frequently noticed in the *tertian*, in which we may find free pigmented hyaline spherical bodies in the plasma, which are parasites, or fragments of parasites, that have come out of the red blood corpuscles. Finally, all the pigmented bodies which in man are sterile, forms of the *anophelic* cycle, end by becoming included when they can not continue their regular development outside the human body The free or included pigment then accumulates in certain viscera, spleen, liver, and bone-marrow, just as do inert powders injected into the circulation. But it is to be remembered that in those organs a large amount of pigment is formed *in situ*, or within their vascular areas, specially in æstivo-autumnal infections, because of the fact already emphasised that it is precisely within the vessels of the spleen, etc., that the adult forms of the parasite accumulate and complete their development, during which process they form a notable amount of pigments. Little by little the black pigment is seen, in these same viscera in which it has accumulated, to become transformed and destroyed ; so that the melanosis entirely disappears in a short time after the cessation of the infection. The exclusive derivation or otherwise from the melanin elaborated by the parasite of the black pigment, which accumulates in the viscera, sometimes to an enormous extent, in persons who have had several attacks of fever is a question which has been the subject of considerable discussion.

It is now believed that the melanosis of the viscera is chiefly the result of the melanæmia, that is to say, it is the result of the black pigment formed, during acute infection, in the circulating blood. In part it has a local origin, that is to

say, it is derived from the slow transformations of the lumps of yellow pigments which are deposited or formed in the spleen and other organs from altered red corpuscles, which in grave infection die before the direct action of the parasite has transformed their hæmoglobin into melanin.

Schmidt, so we are informed by Newmann, was able to demonstrate by actual experiment that this transformation of *hæmosiderin* into a black pigment is one which does not give the *microchemical* reactions of iron. The chemical composition of melanin is but little understood, although its origin is known. Marchiafava and Celli noted the fact that even the finest of the black granules formed within the red corpuscles, and indicating the earliest stage of the transformation of the hæmoglobin, do not give a *microchemical* reaction of iron ; and upon this point all authorities agree. Carbone, as a result of the chemical analysis of the pigment of a melanotic spleen, came to the conclusion, that malarial melanin is for the greater part identical with *hæmatin*. This does not absolutely exclude the possibility of there being other pigments, included with the *hæmatin*, although he maintains that this is not very probable. Such a chemical composition of melanin would be quite in harmony with what is known in regard to its origin. We know, in fact that *hæmatin* is a product of the digestion, both gastric and pancreatic, of hæmoglobin ; and it is therefore natural enough that the malarial parasite, when absorbing the hæmoglobin of the red corpuscles, should also give out hæmatin as a product of intracellular digestion. In other words, we may suppose that the parasite is nourished by the abstraction of the albuminoid constituents from the complex molecules of hæmoglobin, leaving the pigmented portion, that is to say, the hæmatin unused. According to these researches, then, melanin is a transformation product of hæmoglobin, containing iron, but not in one of those combination in which it is demonstrable by means of *microchemical* reaction.

It is generally believed that the melanin is found only in malarial infections.

Dealing with the question as to whether there is a malarial infection without melanæmia, Marchiafava and Celli affirm, as a result of their researches, that they are inclined to the belief that this is the case, having seen cases in which the parasite accomplished all its life-cycle up to fission, without being pigmented. Many other writers, taking these observations as their basis, speak of a variety of malarial infection, caused by a parasite of the red corpuscles, which did not produce pigment. Still later, others began to doubt the existence of a form of malaria without melanæmia, having observed that, even in cases in which an examination of the peripheral blood showed only non-pigmented parasites and in the brain non-pigmented fission forms, in the spleen there were both pigmented parasites and pigments included in leucocytes. An endoglobular parasite, which completes its whole cycle of existence without the production of pigment, has been described by Dionisi. The existence of an infection produced by parasite of the red corpuscles which complete their life-cycle without producing pigment is a well-established fact, indeed, in the case of certain animals, the important instance of this being that of the so-called *Texas fever* of cattle In the case of the human beings, however, it is certain that of late years, in spite of the great abundance of material, no one has ever seen a case of malaria without melanæmia.

We find in the viscera of malarial parasites, in addition to the black pigment, another pigment in the form of yellow or dark-yellow granules or lumps : this is the *ochraceous* pigment, the distribution of which has been reported upon by Kelsch, Kièner, Gaurnieri, Bignami and others, who affirm that it may be found in large amount in the liver and in the spleen, in less amount in the bone-marrow, and scantily in the kidneys. In contradistinction to melanin,

this pigment gives the iron reaction with microchemical re-agent, and is identical with the *hæmosiderin* of New-mann. It may be found in the liver included within the endothelium of the blood-vessel ; but the larger part of it is in Kupffer's cells and the hepatic cells, differing in this from melanin which is never found in the epithelium of the liver.   Frequently the pigmentation is the most intense around the central vein, and shades off towards the periphery of the hepatic lobule. In some pernicious fevers this *hæmosiderin* is so intense and so diffuse that it is more marked than the black pigmentation of melanin. The for-mation of bile pigment evidently uses up all this *hæmosiderin* in the liver. The yellow pigment is found in the spleen within the globuliferous cells or free in the splenic pulp ; in chronic tumours it is also seen, sometimes in large amount, within the vessels and splenic septa, being evidently deposited along the lymphatic tract.   In the case of the kidneys, in rare instances only, we see granules of *hæmosiderin* within the epithelium of the tubules, specially in that of the convoluted ones. The indications for the presence of this yellow pig-ment, in the viscera of persons who have died of pernicious infection, clearly are that not all the hæmoglobin of the destroyed red corpuscles are transformed into melanin by the action of the parasites, but that the acute infection deter-mines the disintegration of a variable number of corpuscles by means of some other mechanism. Mention has already been made of the brassy bodies, which are the product of early necrosis of the red blood-corpuscles, occurring while the parasites are still in process of development. In this alteration of the red blood-corpuscles we see one source of the *hæmosiderin* deposited in the cells of the viscera ; and perhaps it is the chief source during the acute infection. But we are unable to affirm that all the iron-containing pigment, which is sometimes so abundantly present in the viscera of patients with chronic malaria and cachectic, has

the origin. Above all, in grave post-malarial anæmic conditions we may find an abundant *ochraceous* pigmentation of the liver as in some cases of pernicious anæmia. **Now,** as we know that this anæmia may sometimes continue and even progress autonomously without relapses of fever or fresh parasitic invasions, we are forced to the conclusion that the pigment of hæmatic origin is in this case formed by the action of some *hæmolytic* substance as yet unknown.

Now regarding the changes in the leucocytes in malarial fever, we may note that the attention of the investigators from the earliest days of research has been attracted to the presence of leucocytes containing granules or blocks of pigment. We have already seen that the discovery of the malarial parasite was preceded by a series of resarches, one result of which was to distinguish the pigmented leucocytes from other pigmented bodies differing from them, namely, the large pigmented bodies. With this increase in knowledge of the biology of the parasite came a corresponding increase in the comprehension of the *phagocytic* processes which occur in malarial blood. The black pigment was held by Laveran to be taken up by the leucocytes after the disintegration of the parasites. Later, Marchiafava and Celli established the fact that the white cells can take in, not only pigment, but whole parasites and parasite-infected red corpuscles, and observed that the whole phenomenon of *phagocytosis* may also occur, *in vitro*, in ordinary preparations of blood, so that we may witness the struggle even under the microscope. They noted, moreover, that the vascular endothelium also plays an important part in *phagocytosis* in malaria. The importance of the part taken by *macrophagi* in the liver and spleen was later pointed out by Metchnikoff. In the case of *tertian* and *quartan* fevers *phagocytosis* was studied by Golgi who discovered that the pigmented leucocytes are to be found in the blood in the early hours of every febrile attack, and concluded that phagocytosis occurred

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regularly in correspondence with determined phases in the
life of the parasites. He attributed great importance to the
phagocytic action of the leucocytes, holding that it was due to
the spontaneous cure of malaria, as others believed; and he
even went so far as to assert the probability that the fact of
not all the malarial parasite becoming pernicious is due to this
process. Gaurnieri investigated the question of *phagocytosis*
in the liver; and Bignami extended his researches to the
various viscera in pernicious fevers; and both describe the
occurrence of *phagocytosis* leading to the degenerative changes
which occur in the leucocytes and in the endothelium.

Regarding the elements which play the part of *phagocytes*,
these are (*a*) some, but not all, of all the varieties of leuco-
cytes which are in the circulating blood; (*b*) the endothelial
cells and the cells of Kupffer in the liver; (*c*) the cells of the
splenic pulp; and (*d*) the large uninuclear leucocytes, with-
out granulations, in the bone-marrow; (*e*) the chief rôle in
the *phagocytosis* during the febrile attack belong to the leuco-
cytes in the circulating blood; but not every kind of leuco-
cytes has a *phagocytic* function. Although the observance of
small pigmented leucocytes, in rare cases, has been claimed
by Vincent, Guarneri and others, still they have noted that
lymphocytes never contain black pigment. The large uninuclear
leucocytes without granulations, and the so called transi-
tional forms are generally believed to be the most important
agent in this process. Next in order come the ordinary
leucocytes with *polymorphous* nuclei, and *neutrophile* granula-
tions— multinuclear leucocyte; the fact that the greater part
of the phagocytes found in malarial blood belong to the
group of *macrophagi* of Metchnikoff follows from the fact
that neither the *lymphocytes* nor the *eosinophile* white cor-
puscles perform *phagocytic* function, and because it is
altogether exceptional to find a pigmented *eosinophile*
leucocyte. In ordinary malarial affection the total num-
ber of leucocytes diminishes to below normal, while in

pernicious fevers it is increased. But the fact is also worthy of notice that the numerical proportion between the various kinds of leucocytes is more or less markedly modified ; that is to say, there is increase in the large uninuclear leucocytes and the transitional forms, and a diminution in the number of the polymorphous leucocytes, while the number of lymphocytes remains at about normal. This modification in the numerical relation between the large uninuclear leucocytes and those with polymorphous nuclei is found in the ordinary infections *—tertian, quartan, æstival,* as well as in the *pernicious* forms; in the last mentioned, the increase of the large uninuclear cells chiefly attract attention, while in the first attacks of a primary affection it is the least marked. The large number of macrophagi found in some cases is a matter of astonishment to all who examined the blood in pernicious fever ; and, indeed, the increase in the number of large uninuclear leucocytes is much more noticeable in grave malarial infection than in those conditions, such as grave anæmia *hyponutrition* of the organism, in which, as Ehrlich has shown, the same thing occurs. In malarial blood there is an increase of precisely those elements which play the chief part in *phagocytosis,* namely, the large uninuclear cells. These bodies enter into the circulation in a larger number than normal, evidently by a process of *chemotaxis ;* or, in other words, for the same reason that in other morbid conditions multinuclear leucocytes are poured into the blood. The *chemotaxis* is specific, and is exercised in determined substances upon a particular species of leucocytes ; in fact, if an individual in whom malaria alone has determined a percentage increase in the large uninuclear cells, there occurs some inflammatory process, such as pneumonia or erysipelas, the multinuclear cells in their turns increase in the blood—inflammatory leucocytosis—under the influence of the specific action of Fraenkel's *diplococcus* or of the *streptococcus.* (*f*) It is only during the course of the gravest

infection that the pigmented endothelial cells are found circulating in the blood. They evidently become detached from the vascular walls, as a result of the alterations which they undergo after the inclusion of the foreign bodies which they take up. A minute investigation of the viscera can alone give us an exact idea of the extent to which this function of the endothelium is exercised. In some cases the number of pigmented endothelial cells in the brain is remarkable. It is evident that the accumulation of adult parasite in the cerebral vessels, and the resulting relative slowness of the circulation, favour the development of this function. But while this function of the endothelium helps to free the blood-vessels from injurious matters, on the other hand lesions of the vascular walls which increase the difficulties of the capillary circulation and contribute still further to its retardation, are produced by the degenerative changes which follow *ph igocytosis*. A phagocytic action of the endothelial cells is observed even in the liver ; indeed, the pigmentation of the endothelium persists longer than does the presence of melaniferous leucocytes within the capillaries after the active infection has ceased. To this Bignami testifies ; and the same thing has been noticed in the case of Kupffer's cells by Guarneri, who says that he found in them not only the black pigments, but grains and clumps of *hæmosiderin* or yellow pigments in variable amount, but in pernicious fever in considerable quantity. (*g*) In all acute malarial infections the cells of the splenic pulp take an active part in phagocytosis. This is demonstrated not only by pathological studies in pernicious fevers, but also by the examination of the splenic contents extracted by puncture in cases of ordinary fever. The number of pigmented *globuli ferous* and parasite-containing macrophages is truly enor-mous in grave infection ; but no included bodies are eve found in the *lymphocytes* of the *malpighian follicles*. The blood of the splenic vein is rich in pigmented *macrophagi o*

the *débris* of red blood-corpuscles, for which reason it is believed that it is from the splenic pulp that a large number of similar elements which accumulate in the capillary network of the liver are derived. (*h*) Not only within, but also outside of the blood vessels of the bone-marrow, specially of the spongy bone—*phagocytes* of similar histological character are also found in the majority of pernicious fevers. It is certain that some of these elements are derived from the blood which deposits them in the large medullary veins ; but everything points to the belief that in large part they are medullary cells, which have exercised *phagocytic* function *in situ.* That in the spleen and in bone-marrow—and, according to Ehrlich and Lazarus, chiefly in the latter tissues— there originates in this way the large uninuclear cells without granulations—the chief element in the malarial *phagocytosis*— is a fact that is now beyond dispute.

It follows from all these that *phagocytosis* occurs in the whole vascular system during acute malarial infection, but chiefly in certain viscera, and precisely in those which, as experimental pathology teaches us, are deposited in the corpuscular extraneous substances injected into the circulation, *viz*, the spleen, liver, and the bone-marrow. After cessation of the acute infection the *phagocytes* which have gathered up pigments of parasites elsewhere are also deposited in the organs which participate actively in the process by means of their own cells, large uninuclear cells without granulations of the bone-marrow, and cells of the substance of the spleen. There are various kinds of substances which may become included in the cells. The clumps of pigment and the residua of the segmentation, which remains free after the multiplication of the parasite come first in the order of frequency ; less often we find complete fission forms, either free or within *erythrocytes*, or isolated spores. This occurs in *tertian* and *quartan*, as well as in *æstival* fevers. Even in *æstival* fever, the

parasites bring about certain changes in the physical proper-
ties of the red corpuscles, which in all probability favour the
appearance of the function of *phagocytosis*, *e.g.*, as a certain
viscidity of their surface.   As to the young forms and those
in process of development, it is to be noted that only in the
æstivo-autumnal fevers they become included in *phagocytes*
to any marked extent.   The reason for this is found in the
early alterations undergone by the parasite-infected red
blood-corpuscles, in this group of fevers.   In fact, we find
included, in the order of frequency, parasites with central
pigments or peripheral granules of pigments, or even non-pig-
mented young forms contained in brassy or pale corpuscles ;
very rarely, parasites in various stages of development, con-
tained in corpuscles in which the methods of examination at our
disposal do not permit with any certainty of the recognition
of any alteration.   It is rare to find any young parasite
within the leucocytes in the case of tertian fever.   The
pigmented hyaline spherical bodies, which originate from
parasites that have come out of red blood-corpuscles and
have in the plasma become disintegrated, have been seen by
Bastianelli and Bignami, included, in the leucocytes in the
spleen of tertian-fever patients.   From this it is evident
that phagocytes may take in not only the adult and actively
multiplying bodies, which in the process of multiplication
leave the red corpuscles and become free in the plasma,
but also forms in process of development young bodies,
whenever the red corpuscles, which contain them, undergo
some early and profound change which causes them to
behave towards the *phagocytes* like foreign bodies in the
blood current.   The reason why the *phagocytosis* of the
parasite infected red corpuscles is of great importance
only in the group of æstival fevers is obvious from
this early necrosis of the red corpuscles occurring with
regularity in æstival fevers and only exceptionally in the
others.

The *phagocytes*, in addition to these bodies, may take up the adult forms incapable of multiplying in the human organism, that is, the *gametes*. When the latter remain in the host, they go on to those degenerations which were recognised before their subsequent development in the intestine of the mosquito   We find a variable number of fragments of red corpuscles, which, by further transformation of the *hæmoglobin*, give rise to grains or clumps of *hæmosiderin*, in the phagocytes, specially such as are situated in the viscera. In the spleen and liver, specially in the endothelium and in Kupffer's cells, this occurs extensively in the case of certain pernicious fevers.

In short, phagocytosis acts, firstly, on substances which originate from the parasites, that is to say, the black pigment and the residua of segmentation; secondly, on the parasite themselves when they become free in the plasma, or when they are contained within much altered red blood corpuscles; and, thirdly, *débris* of red blood corpuscles and entire dead cells   Phagocytosis is escaped by the parasite-infected red corpuscles which have not been specially changed. Evidently, a chemotactic action between the phagocytes and the substances which they take up, an action which is developed only under the conditions mentioned, gives rise to the phenomenon. There are various modifications which the included substances undergo. The hæmoglobin of the amœbiferous red corpuscles goes through the changes which have been described until the latter are mere shapeless rusty masses. The melanin, which in the leucocytes of the peripheral blood is found in grains or needles or distinct blocks, becomes gathered into large formless masses. These are usually found in the phagocytes of the spleen and liver, while in the circulating blood they are seen only in grave infections, chiefly in pernicious fevers. As to the included parasites, they remain clearly recognisable, and capable of staining ; so long as the red

blood-corpuscles, with which they have been absorbed, persist. The free bodies apparently change and disintegrate very rapidly after their inclusion, so that it is difficult to recognise them; only the fission forms, the bodies with blocks of central pigment, and also the free spores, maintain for a length of time, as yet undetermined, their normal capacity for staining. It will not be possible to recognise parasitic bodies within the leucocytes, if a spleen be examined, with even the best colouring matters, not so very long after the cessation of an acute infection. It is probable, then, that all the parasites included in white corpuscles are destroyed with more or less rapidity, and become incapable of further development. Only as to the spores which remain recognisable longer than the other parasitic bodies, Bignami advances the theory that they may persist alive and take on a new development after necrosis of the white cells which contain them. He also further supposes that the said spores, which are naked in the beginning, may later become surrounded by a membrane, and thus, when still within the leucocytes, escape our methods of staining and demonstration. It is impossible at the present time to refute these hypothesis advanced for the explanation of the period of latency, although they have received no confirmation from the researches of others.

The theory of Golgi and Monti, that the æstivo-autumnal parasites are capable of continuing their development within the leucocytes or the tissue cells, may be positively excluded; and opposed to it are all the arguments derived from probability and analogy. The chief argument in support of this theory is the fact that within the phagocytes may be found every phase of the parasite from the youngest to that of sporulation; yet, as has been already mentioned, the number of young parasites included is small in comparison with the number of bodies with central pigment or in fission; so that it is erroneous to

assume that the adult bodies come from the parasites which have been included in the leucocytes from the earliest stage of their existence. On the other hand, direct observation shows that most of the parasites become included only in the later stages of their life-cycle which had developed normally within the red blood-corpuscles. Degeneratic changes, which may go on to necrosis, frequently occur in the leucocytes as well as in the other cells that have acted as phagocytes. These alterations may be seen in the leucocytes which are found in the peripheral blood only in grave infections and in pernicious fevers; as a rule, they are seen also in the spleen, liver, and bone-marrow, where, indeed, there is an abundant presence often of the degenerating and necrotic elements. Fatty degeneration and nuclear changes are the principal alterations to be observed. The former attacks chiefly the large uninuclear leucocytes and usually after they have taken in large numbers of foreign bodies; they then appear as large cells, even two, three, or more times the normal size of an ordinary leucocyte, which contain in their protoplasm a large number of spherical shining bodies of various sizes, which in fresh preparations are sometimes oscillating, which disappear in dried preparations, are not stained by anilin colours, and are not visible in sections fixed in alcohol. A similar degeneration may be seen, although rarely, in leucocytes which do not contain other bodies. Bignami found the same change, in some cases of acute malarial infection in the endothelial cells of the spleen and liver, and in Kupffer's cells. For the most part these little spherical droplets are of a yellowish colour ; sometimes the yellowish colouration is seen throughout the whole cell, suggesting a slight imbibition of hæmoglobin, such as has been noted to a greater or less extent in the leucocyte in certain cases of intoxication by *hæmolytic* poisons, such as *pyrodin*. This special form of alterations may be studied in preparations fixed in *osmic*

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acid ; in them we note that the granules or droplets scattered
in the protoplasms have generally only their outlines darkened.
Although they would appear to be fat droplets—from their
other properties, such as solubility in alcohol and ether—
this fact makes it difficult to determine their exact nature.
It is the macrophagi that, as in the case of fatty degeneration,
are chiefly attacked by vacuolisation : in this case also, the
cell is swollen, and the protoplasm appears to be rarified
by the presence of numerous vacules, in some of which we
may see included bodies. This alteration may also be seen,
in circulating blood, specially in grave cases of æstival fever.
The nucleus may sometimes show retrogressive changes ; in
other cases in the leucocytes with vacuoles, as in those with
fatty degeneration, the nucleus often remains in normal
appearance in stained preparations. We often do not see
it present at all in fresh preparations ; and we are sur-
prised to see these protoplasmic masses of occasionally
enormous size, filled with vacuoles, without perceptible nuclei,
and sometimes presenting active amœboid movements.
When examining a fresh specimen at a temperature above
85° F., preparations fixed in absolute alcohol and ether, and
stained with hæmotoxylin and eosin, show well the nuclear
changes. Sometimes the nucleus is fragmented in irregular
masses, which become intensely stained in a somewhat uni-
form manner—nuclear fragmentation and *chromatolysis*. At
other times only the membrane of the nucleus is recog-
nisable, the nuclear chromatin having disappeared, and the
whole nucleus is but faintly stained. From this change, a
series of transitional *stages* lead up to the *phagocytes* which
represent all the signs of necrosed element, that is, coagula-
tion necrosis ; they are formless masses of protoplasm, with
irregular outlines, without trace of nucleus, staining faintly,
and sometimes dotted with irregular small bodies that are
stained with hæmotoxylin, and represent residua of the
nuclear chromatin. In preparations from the spleen, we see

also protoplasmic masses of varying size, without recognisable cellular structure, formed, it is believed, by the necrotic phagocytes undergoing fragmentation The endothelial cells present similar alterations, while many phagocytes undergo these retrogressive changes, which partly account for the *leucopania* observed during the febrile attack of malaria, other cells multiply actively in the *hæmotopoietic* organs. Multiplication by *karyokinesis* of the endothelia and Kupffer's cells has been observed by Guarneri and Bignami in the liver: the latter further described the multiplication by *karyokinesis* of the cells of the splenic pulp, and of the large uninuclear leucocytes of the bone-marrow. The new elements replace those which have become necrosed from the exercise of their phagocytic functions. It is to be noted that the cells in karyokinesis are, as a rule, non-pigmented. In pernicious infections *karyokinesis* of leucocytes may occur even in the circulating blood, as has been observed by Bastianelli and others. The process is exactly similar to those seen in the splenic pulp and in the bone-marrow. In some pernicious fevers these forms are somewhat numerous, two or three being formed in one preparation ; but they are always less in number than in preparations from the splenic pulp By this active proliferation on the *hæmatopoietic* organs provide an abundant supply of new large uninuclear leucocytes, of those elements which are of chief importance in malarial *phagocytosis*. As in grave anæmic conditions *erythroblasts* in *mitosis* may issue from the hæmatopoietic organs, a similar thing may happen with the corpuscles (white) in malaria ; in other words, immature forms of these elements may be poured out into blood, in consequence of the infectious process the loss of these being greater.

In the case of tertian and quartan fevers, the development of the phagocytic function is in intimate relation to the life-cycle of the parasites and to the evolution of the fever ; such has, indeed, been proved by the researches

of Golgi.   According to him, we shall look in vain in the circulating blood for manifestations of *phagocytosis* in regard to the malarial parasites when the latter are in their endoglobular stage, and even when they are found in the phase preceding their perfect maturation ; on the other hand, we can readily perceive the phenomena of *phagocytosis* when the parasites have reached maturity, and are about to become segmented or have already divided.   They begin with the onset of the attack, are most evident from three to four hours later, and terminate a few hours after the end of the attack, but even later there are events which seem to represent the continuation of the process ; the phenomena, in their entirety, occur in a period of from six to eight or twelve hours.   He describes as existent in the blood, during the period of development of the attack, white corpuscles containing bodies in process of segmentation, or with well-formed spores, or isolated masses of pigments.   Later, there are in the blood leucocytes containing the same malarial bodies in a more advanced stage of disaggregation.   The destruction of matter is accomplished after ten or twelve hours ; and in the next attack these *phagocytes* which now disappear undergo the same changes.

The following law is formulated by Golgi on these facts : " Phagocytosis is a process which develops periodically like a regular function of the white cells, a function which develops in a certain manner corresponding to determined phases in the evolutionary cycle of the malarial parasite and in a certain period of each febrile attack." From what has already been said, it is evident that phagocytosis occurs throughout the vascular system, but preferably in certain viscera, such as the liver, spleen, etc. ; for which reason what is seen in an examination of blood from the finger should be regarded as a mere episode in this process which, at least in this group of fevers, is chiefly carried on in the internal organs, so that we

are unable to state that the process is not taking place else-where, we do not find examples of phagocytosis in the peripheral blood. The phagocytic bodies, specially the leu-cocytes including the round masses of pigment found at the centre of fission forms, in summer tertian fever begin to appear at the onset of the attack, and during the attack they usually increase in number until towards its close they become exceedingly numerous. In typical cases of æstiva tertian, the largest number of pigmented white blood cells is usually seen at about the time of the precritical elevation of temperature. During the brief period of apyrexia, the phagocytes diminish to a notable extent; and in rare cases they disappear, and at the beginning of the next seizure they are seen to be more numerous. In almost every case one can prove these occurrences: indeed, there are some cases of mild æstival tertian fever in which for a short time no parasite can be found in the peripheral blood, but in which the presence of pigmented leucocytes allows of an accurate diagnosis of the disease. In cases of infection of recent date, one may easily follow the cyclic function of the white corpuscles, which is accomplished in correspondence to the febrile attacks; but it is not seen in cases in which the malarial infection has lasted for some time. The brevity of the periods of apyrexia increases the difficulty of deciding when the leucocytes, which are found in these cases always, increase or diminish. It is not difficult to explain why in these cases phagocytes should be found in the blood not only during and shortly after the febrile attack, but also during the whole period of apyrexia. It is well known that when the acute infection ceases, the phagocytes slowly leave the general vascular system of the viscera, lungs, intestines, kidneys, etc., and collect in the spleen, liver and bone-marrow.

Now, experience has shown that this purification of the circulation takes for its completion many hours and in some cases several days, according to the gravity of the

parasitic invasion : we can therefore understand that, during the period of apyrexia interposed between two attacks, we should continue to see phagocytes circulating in the blood, because of a succession of febrile attacks, numbers of them have polluted the capillary system of the viscera.   The presence of the pigmented leucocytes in scanty number in the blood for several days, five or six after the parasites have disappeared, in the apyrexia between a series of relapses, can be accounted for in the same way.   As a rule, the phagocytes are exceedingly numerous in the majority of pernicious-fever cases.   We are more liable to find in these grave infections than in the ordinary æstival-tertian in addition to the pigmented leucocytes, phagocytes containing complete sporulation, and parasite-infected brassy bodies, pigmented and globuliferous endothelial cells, etc.   The presence of the large macrophagi, which have been already described, and some of which show degeneration, as the most striking features of these cases, for five, six, or eight days after a cure with quinine, we generally see phagocytes circulating in the blood.   If the parasites and phagocytes were numerous in the blood before the exhibition of the remedy, after the fever has been cured by the quinine, the pigmented leucocytes are seen in the circulation for a variable time, even for days. During the action of the drug, we often are able to perceive an increase in the number of the pigmented and globuliferous leucocytes the reason for which is found in the fact that the phagocytes seize all the parasitic bodies, the development of which has been arrested by the quinine ; and that, moreover, the transformation of the red corpuscles into brassy bodies is favoured by the medicament itself whence there is an increase in the amount of material which the phagocytes might seize.   It is more perfectly in pernicious fevers than in ordinary infections, and, what is worthy of note, not only in pernicious fevers which are destined to recover, but in those which have a fatal ending,

that this increase in phagocytosis after the administration of quinine is observed. No constant results are forthcoming from a careful examination of the blood in cases in which a spontaneous cure has occurred. Sometimes when the attacks have become weaker and finally disappeared, one may see an increase in the number of phagocytes as compared with that seen in the days preceding those in which the infection tended to become spent : on the contrary, the diminution of pigmented leucocytes appear to keep pace with the disappearance of the parasites in other cases. When there is a persistence of crescent bodies in the blood after the cessation of the fever, we continue to see pigmented leucocytes at intervals, just so long as the crescent bodies are present ; not infrequently we also see included round bodies with pigments in wreath form, or true crescents. The fact that in these cases the pigment contained within the leucocytes is in fine needles or rods, so that we can be sure that it has come from degenerated and included crescents, is particularly noteworthy. We also see that, on comparison of these facts with those observed in *quartan* and *tertian* fevers, even in *æstivo-autumnal* fevers, the most intense phagocytosis corresponds to the period in which the parasites are multiplying. But there are some differences, which are indicated by what has been said above. In the first place, in grave fevers we often find globuliferous cells, and specially macrophagi, containing parasite-infected brassy bodies. The included red corpuscles may be entirely decolourised, or may appear almost normal ; they may contain young non-pigmented plasmodia, or pigmented forms, or small bodies with central pigment in fission, or bodies of the crescent stage. Consequently, the parasites, even when they are in the phase preceding their full development, and also when they are endoglobular, may in grave fevers present the process of phagocytosis. It appears certain that the special modifications which the parasite-infected red corpuscles may

undergo in this kind of fever partly explain their inclusion within the leucocytes, an inclusion which may occur even when much of the parasite-infected globule survives. The *tertian* and *quartan* parasites, as we have seen, do not present in their corresponding stages these changes ; and in them, also, in the case of grave fevers, we note with less distinctness the periodicity of phagocytosis. The reason for this difference is found in the shortness of the period of *apyrexia* in æstival fevers, the fact that in these fevers the multiplication of the parasites from which is derived the greater part of the substance taken up by the phagocytes occurs chiefly, if not exclusively, in the internal viscera, and, finally, in the greater tendency towards an irregular clinical course of these affections.

It is apparent, then, that in malarial fever phagocytosis is of great importance. But, if we attempt to ascertain which part phagocytosis takes in the defence of the organism against the parasitic invasion, what influence it exerts upon the course of the infection, and if it is due to spontaneous recovery, we come against many difficulties in the interpretation and comprehension of the facts. For this reason it is not to be wondered at that the reports of various investigators do not agree. Some accord to phagocytosis a secondary place, while others hold that it is mainly responsible for the defence of the organism and the production of immunity of malaria. Nevertheless, the function which belongs to the phagocytes of clearing the vascular system from the detritus and dead corpuscles, deposited during acute infections, is a fact beyond doubt. When we think of the large amount of black pigment that is set free in all parts of the vascular system in some pernicious fevers, and of the great number of degenerated red corpuscles and of free parasites which become included in endothelial cells and in leucocytes, and recall the fact that all these matters are deposited in certain viscera, the spleen and liver chiefly, in the course of a few

days, we are able to realise the importance of the function.
In a relatively short space of time, the vascular system of
the most important viscera, as, for instance, the brain is
resorted to, conditions essential to a normal circulation of the
blood. We may add that the return to a normal condition of
the spleen, and liver, and bone-marrow, in which the *débris* of
the infection is deposited and remains for a while, is in part
the result of a series of phagocytic processes, which are
accomplished slowly and in regular succession. In the
course of acute infections there occur, in certain organs,
degenerative changes in the cells of the parenchyma, and
even more or less extensive necrosis of the tissue, this
having been observed chiefly in the spleen and liver. In
the case of the liver, where the process can be clearly
observed, Bignami has shown that these necrosed areas are
eliminated and replaced by a tissue of new formation, which
originates in the special cells of the organ itself only when
the whole vascular system of the necrotic area has been freed
and cleansed from the foreign bodies deposited therein.
The cleansing of the pigment and of the foreign bodies
deposited during an acute infection occurs more rapidly in
the bone-marrow than in any other organ. Indeed, as
Bignami noted in sections from cadavers of persons dying at
varying periods after the cessation of the infection, we find
that the marrow contains a scanty amount of black pigment
or scarcely any, in cases in which the melanosis of the
spleen and liver is still intense. Now, this return to the
normal, which cannot help having a beneficial action upon
the activity of the bone-marrow as a hæmopoietic organ,
is ultimately the work of the phagocytes. By reason of the
return to the normal condition of the tissues affected through
their agency, we find their importance to be great even
limiting the function of the phagocytes to that of *spodoferous*
and *spodophagous* cells. The question as to whether the perni-
cious infections are such because of deficient phagocytosis,

and the mild infections, mild by reason of the energy of this process has been much debated.   In these researches into quartan and tertian fevers, Golgi was held to attribute an importance to phagocytosis from this stand-point which is not generally admitted.   He noticed that during each febrile attack the leucocytes contained not only the retrogression products of the parasites, but also a certain number of parasites themselves.   If this were not the case, and if all the parasites invariably completed their life-cycle, then, according to him, every case of intermittent malarial fever would go on increasing in severity even to the point of transformation into pernicious fever, which, as we all know, is not the case.

Indeed, it cannot be admitted from actual observation that phogocytosis is the only factor in preventing the aggravation of all cases of fever, and specially the conversion of quartan and tertian into pernicious forms.   In fact, from the time that the parasite of quartan and tertian infections have been known there have been no examples of pernicious fever caused by them.   This, as we have observed elsewhere, leads one to attribute this constant fact to the biological properties of this group of parasites, and not to functions of defence and individual reactions which are so apt to be variable in their action.   The virulence and toxicity of the parasities in this group are specially productive of pernicious fevers, which are caused only by the parasites of the æstivo-autumnal variety.   The part played by the phagocytosis in spontaneous recovery from the disease has been subjected to much disputation.   In the case of grave infections it is not true that some of them become fatal because of insufficient phagocytosis, and that others are cured from the efficacy of this defensive process.   A close examination of the facts shows that there are fatal pernicious fevers with extensive phagocytosis, and others in which the process is feeble ; the first occur usually in relapses of malaria, the second in primary infections.   As a rule, phagocytosis is very

active in grave infections, so much so that up to a certain point we may consider the number of phagocytes to be in proportion to the number of parasites; in other words, phagocytosis is most active when there is the greatest number of parasitic forms in the condition necessary to admit of their being taken up and included, as has been already described. This condition of things warrants the belief that the result of these infective diseases is in part dependent upon the primary number of parasites, and is in part under the control of a complex series of factors which in their entirety constitute what is known as the power of resistance of the organism. It is generally thought that it is the unjust feeble simplification of a very complex process to attempt to explain the resistance and relative immunity, acquired by many patients with malaria during the course of an infection, by phagocytosis alone.

Kidneys in malarial cachexia.—In chronic malaria these organs do not, as a rule, show any great changes. The *congestive* and the *atrophic* are the two forms of kidneys described. The former, the engorged kidneys, are of large size and increased in weight ; the surface is smooth, the consistency firm, and the colour deep red. The congestion is specially marked in the pyramids. All the vessels are distended, and the congestion is sometimes so extreme that interstitial hæmorrhages may result, or hæmorrhages into the interior of the tubules. The epithelium of the latter is granular ; there is often desquamation, and the presence of hyaline casts may be noted   On the other hand, the atrophic kidneys are small, and irregular in outline. The capsule is adherent, the consistency increased, the kidneys show a maroon or mahogany colour, or a blotchy appearance. Small cysts are often to be found. Both the epithelium and the connective tissue of the tubules show alterations. Chronic malaria is sometimes followed by amœboid degeneration. This

has been noted in the kidneys by Laveran (Traité des Fievres palustres, p. 94) in two instances, but in both of them the malarial cachexia was complicated by chronic broncho-pneumonia and bronchiectasis. Frerichs (Lehrbuch der Leberkrankheiten) describes three cases, while Marchiafava and Bignami (Riforma Medica, 1891, in p. 571) have carefully studied several instances. The distribution of the amœboid substance in their cases, was as follows: the degeneration was most prevalent in the kidneys, where not only the vessels of small and medium size and glomeruli were affected, but also, to a considerable extent, the walls of the renal tubules. Of a very grave character are the degenerations of the renal parenchyma and the alterations of the interstitial tissue. Next to the renal organs, the amœboid degeneration is most severe in the intestines and the spleen. In the intestine the degeneration affects chiefly the vessels of the villi, but also the vessels of the submucosa, and to a less extent those of the other intestinal coats. In the spleen the vascular network of the periphery of the follicles is particularly affected. Here one sees usually the deposition of great blocks of amœboid substance, while in the traberculæ of the pulp the process is in its beginning or is entirely wanting. In the liver there is a less extensive and diffuse deposition of amœboid substance than in the kidneys. The degeneration affects islands of hepatic tissues which are irregularly disseminated ; so that, for example, one may see an island of the size of a lobule, or larger, from which hepatic tissue has entirely disappeared, the vascular network showing that there is a grave amœboid degeneration, while about this the hepatic tissue has a normal appearance. The alteration in question spreads from the periphery of the hepatic lobules, where the small areas of degeneration are first to be observed.

Malarial cirrhosis.—With malarial fever there used to be associated hepatic cirrhosis, chronic renal lesions, and, in

some instances, chronic inflammation of the lungs, endocardium and central nervous system. Indeed, in almost all works upon medicine, malarial fever is included as one of the etiological factors in ordinary atrophic cirrhosis of the liver. This statement has been based almost entirely upon rough clinical observation. No one having definitely traced the development of the cirrhosis from changes following acute or chronic malaria. Frerichs (*Loc. cit*) noted the rarity of cirrhosis in patients dying with chronic malaria, though in five instances this was the only etiological cause which he could discover. Laveran (*Loc. cit,* p. 90) in his considerable experience has seen but two cases of atrophic cirrhosis following malarial fever, and Welch only one instance of this. Two forms of chronic malarial cirrhosis and three of chronic malarial hepatitis are recognised by Kelsch and Kièner, who described them at length, namely, *Insular cirrhosis* with nodular hepatitis and insular cirrhosis with diffused parenchymatous hepatitis ; and annular cirrhosis with nodular or diffuse parenchymatous hepatitis. The general appearance of the liver is that of ordinary atrophic cirrhosis in these cases. The development of ordinary chronic hepatic tumour in malarial cachexia is described by Bignami, who concludes that there is little evidence to show that ordinary atrophic cirrhosis is a frequent follower of the disease, and remarks that it is easy to understand from this that it is " not difficult to make a differential diagnosis between this form of chronic tumour or of chronic hepatitis, as one might say from the other forms of cirrhosis ." There are no facts or reasons sufficient to cause us to believe that ordinary cirrhosis can follow a chronic tumour. The structure in the two cases is absolutely different. In the one we have an extensive new formation of connective tissue, multilobular in nature, retracting about the included lobules ; in the other, a more scanty formation of perilobular connective tissue about a single lobule, not contracting, together with grave alterations of

the lobules themselves, especially of their vascular and lymphatic system, not depending, as we have seen, upon the new formation of perilobular connective tissue, but due to lesions primarily local. Atrophic conditions of the liver exist in malaria, but are simple atrophies, and occur in patients who are exhausted, for example, by profuse diarrhœa, etc., or in cases of progressive post-malarial anæmia. The complete want, or almost complete absence, of any process tending towards the regeneration, resulting from grave and diffuse retrogressive lesions, may be taken as responsible for their occurrence The fact that many conditions exist in the organs in malarial fever, which might well be the starting-point for extensive growth of connective tissue, has been emphasised by Barker (John Hopkin's Hospital, Reps., Vol. V) who at the same time discusses the relations of malarial infections to the cirrhotic process. The development of characteristic cirrhosis of the liver and of the kidneys in rabbits following focal necrosis not dissimilar to those found in the liver in acute malarial infections, has been observed by Flexner (Med News, Aug. 1894) after the injection of blood serum from one animal into another. Though the possibility of its occurrence cannot be denied, the question of the possibility of the development of a true cirrhotic atrophy of the liver, of malarial origin, is not settled ; the development has never been actually traced, and the condition, if it exists at all, is probably rare.

Heart in malarial cachexia. — As a consequence of anæmia and recurrence of fever the muscular tissue of the heart suffers. The heart muscle degenerates, the ventricles dilate, thus eliciting a clinical evidence of functional derangements of the heart and proceeding to an advanced stage, the lower extremities become œdematous.

CHAPTER XIV.

INCUBATION, CLASSIFICATION, CLINICAL
COURSES AND VARIETIES

INCUBATION.

The duration of the period of incubation of malarial fever has been variously described by those who have given the question to special study. It has undoubtedly been observed that characteristic malarial fever may appear very shortly after exposure in a malarious district, many observers believing that this may occur within a shorter time than 24 hours. It is possible that the febrile attacks which may occur sometimes immediately after exposure at night in damp, marshy, malarious districts may have some other cause than malarial infection. Thus, Plehn describes cases where, after exposure at night in very malarious districts in West Africa, there was an immediate paroxysm similar to a malarial attack, which did not recur until the appearance, ten days later, of a true malarial fever, which doubtless dated its infections from the night exposure. At the time of the first paroxysm the examination of the blood was negative, the parasite æstivo-autumnal) not appearing until ten days later The hypothesis of Plehn that the initial paroxysm was due to the absorption of some toxic substance produced, perhaps by the parasite outside of the body, seems a little far-fetched. More commonly an interval of one or two weeks may be made out between the time of exposure and the time of the breaking out of the disease. Hertz (Ziemssens Ency., Vol. ii. p. 588) states that the period of incubation is commonly reckoned at from 6 to 20 days, but believes that the disease may appear immediately after the entrance of the virus into the system. Maillot (Treatise on Fevers, p. 263) considered the mean

period of incubation to be from 10 to 12 days; while Sorel (Arch. de Med., Milit., 1884, T. 3, p. 273) estimated it at from 7 to 9 days. A perusal of the literature of the disease will show that many exceedingly long periods of incubation have from time to time been reported, though many of them are open to considerable doubt. Such, for instance, is the case of Blaxall (cited by Hertz, *loc cit*), where after spending five days in the harbour of Port Louis, two of the crew of a man-of-war were attacked, at the end of 12 and 14 days respectively, with quotidian intermittent fever, while two others developed tertian fever at the end of 48 and 184 days respectively, after enbarkation. In view of our present knowledge, it is probable that many cases of prolonged incubation represent relapses of earlier attacks, the mani-festations of which have been present and would have been recognised had the patients been properly observed by those who had to come in contact with them. The question has been studied in a more intelligent manner of recent years since the discovery of the germ of the disease, and the inoculation experiments of Gerhardt, Mariotli and Ciarrochi, Marchiafava and Celli, Gualdi and Antolessi, Angelini, Di Mattei, Galandruccio, Bein, Bacelli, and Sacharov. The period of incubation in these cases, where the blood of one malarial patient was introduced intravaneously or hypodermically into a healthy individual, have varied greatly. In individual cases there was a variance in the period of incubation of from 6 to 18 days, while the average duration was from 11 to 12 days. More recently, Bastianelli and Bignami have contributed four new cases to this list, and have given careful attention to the subject. The period of incubation in their cases of artificial inoculation represents the time necessary for the inoculated parasites to arrive, by multiplication, at the quantity neces-sary to determine the fever. The period of incubation, with a given variety of parasites, varies inversely to the

quantity of material inoculated. The mean and minimum period of incubation, under equal conditions, varies with the various groups of the fever; it is least with æstival fevers, a little longer with tertian fever, and yet longer with quartan fever. They believe that they are justfied in concluding that the period of incubation in experimental malarial infections is not a constant quantity, but varies in the same group of fevers and in different groups. In a given group of fevers it depends primarily upon the quantity of material inoculated. They say that in different groups of fevers it varies with the special capacity for reproduction of the parasitic variety and with the rapidity of the cycle of development of the parasite of the disease. After analysing their cases, they conclude that in quartan fever the maximum duration of the period is 15 days, the minimum 11, and the mean 13; in tertian fever, the maximum 12, the minimum 6, and the mean 10; whereas in æstivo-autumnal fever the maximum is 5, the minimum 2 and the mean 3 days. We may take it then that the incubation period in æstivo-autumnal fever may be as brief as two days; and this fact is well worth noting. As we do not know how or in what form it occurs, we cannot positively assume that these figures represent the period of incubation in infection as it ordinarily occurs. It is striking to see how well their conclusions agree with the deductions which have been drawn by other observers before the discovery of the malarial parasite. It is with the æstivo-autumnal variety of the parasite, that is associated with the pernicious fevers, that the short periods of incubation have been observed, while the older clinical observations of short periods of incubation relate to the same class of cases. The facts of clinical observation agree quite closely with the general results of inoculations in tertian and quartan fevers, while the demonstration that the disease may appear in 48 hours after small intravenous inoculations makes us believe that the true incubation period may be extremely

short in some very malignant fevers, however the infections
may take place.   To account for certain early manifestations
of the fever Plehn (Virchow's Arch., 1892, CXXIX, 285)
propounds   a   very   ingenious   theory   As   already men-
tioned, he asserts that he has noticed in several instances
a well-marked febrile reaction occurring a few hours after
exposure in malarious districts, and simulating a single
malarial paroxysm.   The examination of the blood was nega-
tive.   From 9 to 12 days later, characteristic malarial fever
developed, the parasite being readily found in the blood.   He
suggests that by exposure in extremely malarious districts
the individual may absorb a sufficient quantity of a *pyrogenic*
toxin to cause immediately a single paroxysm days before
the true incubation period has been passed through.   This
theory, however, is not generally entertained.   We may take
it, then, that, basing our conclusion upon the comparison
between clinical deductions and the accurate observation of
inoculation experiments, it seems likely that the ordinary
period of incubation in tertian fever is about 10 or 12 days,
in quartan fever a little longer, while in æstivo-autumnal
fever the period in question probably averages a somewhat
longer time than in both these varieties of the disease, rang-
ing from 24 hours, or even less, to 10 days or two weeks.

CLASSIFICATION.

There are two principal groups of malarial fever, *viz.*,
first, the *regular intermittent fevers*, occurring throughout the
malarial seasons ; and, second, the more *irregular*, often
more or less *continued fevers*, occurring only at the height
of the malarial season, the late summer and autumn.   In
temperate climates, nevertheless, one may separate three
distinct types of fever under these main classes, depending
in turn upon infection with one of the three types of the
malarial parasite which have already been described.   Thus,
the first class, the *regular intermittent fever*, includes :

(*a*) *tertian* fever with its combinations (double tertian fever), and (*b*) *quartan* fever, with its combinations (double and triple quartan fevers). The second class of fevers, that including the more *irregular* varieties, occurring as it does at the height of the malarial season (August, September, October), justly deserves the name (*c, œstivo-autumnal* fever, which the Italian physicians gave to it long ago; it depends upon infection with the third variety of the malarial parasites previously described. Almost all malarious localities furnish instances of *tertian* fever. The *quartan* variety, however, is rare in many districts where the other forms of infection are frequent. There are certain regions, however, such as in certain parts of Sicily and in the neighbourhood of Pavia in Italy, in which quartan fever is particularly common. In the United States of America it appears to be rare; thus, out of nearly a thousand cases observed at the John Hopkin's hospital, only nine cases of *quartan* fever have been observed. In India it also appears to be very rare, though one is not surprised to see a case now and then in highly malarious localities, especially in Terai. Wherever they exist, these types of the disease are the same The milder forms, tertian and quartan fevers, alone prevail in districts where malaria is very uncommon. In tropical countries the severer types of *œstivo-autumnal* fevers are in excess. As one passes away from the Equator, only the milder tertian and quartan fevers are to be seen in the earlier parts of the malarial season while the æstivo-autumnal fevers appear in the later part of summer and early autumn.

Tertian fever.—This form of malarial fever admits of two varieties, *viz.. single infections* or *tertian intermittent* fever, and *double infections* or *quotidian intermittent* fevers.

Single Infection.—*Tertian intermittent fever.*—Infection with the tertian parasite is responsible for this type of malarial fever. This organism has already been described, and possesses the remarkable characteristic of existing in the

blood of the infected individual in great groups, all the members of which are approximately at the same stage of development, and pass through their cycle of life together, all the organism composing this group undergoing segmentation within a period of several hours ; it requires, as has been said, approximately 48 hours to complete its cycle of development. In infection, then, with a single group of parasites segmentation occurs at intervals approximately 48 hours apart.   As Golgi so clearly showed, the febrile paroxysm is always associated with the segmentation of a group of malarial parasites, and, as one might expect, the chief characteristic of this type of fever consists in intermittent febrile paroxysms occurring every *other* day.   The regularity with which these paroxysms recur is truly remarkable, the onset sometimes taking place at almost exactly the same hours day after day. More frequently there are slight differences, generally, however, of more than two hours, between the time at which succeeding paroxysms recur.   Slight anticipation in the hour of onset is more common than retardation in the opinion of most observers.

Clinical courses.

The *chill*, the *fever*, and the *sweating* are the *three* well known *stages* into which the paroxysm of this type of malaria is divided.

1st stage.—There may be no premonitory symptoms to usher in the chill.   More commonly, for a period of from a few minutes to half an hour, the patient complains of uneasy sensations, a slight headache, or perhaps a little giddiness or fatigue.   Not infrequently the onset is preceded by yawning. If the temperature is carefully noted during this period, it will usually be found that a slight elevation has already begun to appear. Immediately after this, the patient begins to complain of chilly sensations, usually up and down the back ; these increase, the patient begins to shiver, and soon a general shaking chill follows. The chill is often extremely violent ; the teeth chatter ; the whole body is

thrown into so violent a tremor that the bed and often surrounding objects in the room are shaken. The skin is pale, or often somewhat cyanotic and cool, though wholly disproportionately so in comparison to the intense feeling of cold complained of by the patient. It is often moist, while the erection of the hair follicles give rise to the characteristic *cutis anserina* or " goose skin." The pupils are usually dilated. The patient complains of headache, buzzing in the ears, vertigo, and sometimes of visual disturbances. The pulse is small and rapid, and often of rather high tension. There may be a nausea and vomiting. The duration of the chill varies materially in different cases: it may last as long as an hour, though usually the period is considerably shorter, from ten minutes to half an hour. Not infrequently no actual shaking occurs, the patient complaining only of a chilly sensation. Occasionally, though very rarely, in this type of fever, the chill may be entirely absent. During this period of the chill the temperature of the patient rises rapidly, and, at the end of the chilly sensations, may have reached almost its height. Within two hours after the onset of the paroxysm, as a rule, almost the maximum point of pyrexia is attained.

2nd stage.—The *febrile* or *pyrexial stage* is the next to appear. The chilly sensations, after a certain length of time, become less marked and are interrupted by flushes of heat, which become more frequent, and finally wholly replace the chill. Then begins the second or febrile stage of the paroxysm. The patient complains of an intense burning heat ; the skin is flushed, hot, and dry, the conjunctivæ injected, the pulse becomes fuller, but remains rapid : it may be *dicrotic.* The patient complains bitterly of headache, and often of vertigo, and buzzing in the ears. The coverings of his bed, for which but a short time ago he had begged, are now thrown aside, often there is intense thirst. The patient is frequently restless, throwing himself from one side of the bed to

another. In some instances there is active delirium. It has
been known for a patient to jump out of the window of the
ward or house during the febrile stage of a double tertian
paroxysm, and be killed by the fall. In other instances the
patient is dull, drowsy and typhoidal in appearance, com-
plaining upon inquiry only of intense headache and aching
pain in the back and extremities. In certain cases there
may be *epistaxis*. Sometimes vomiting and diarrhœa are
observed. Not infrequently there is a slight cough. The
patient's face is flushed, the conjunctivæ are injected, and the
tongue is often dry and coated. There is often a dusky,
yellowish grey colour of the skin, while the lips and mucous
membranes are pale. Herpes on the lips and nose is very
common. Various cutaneous eruptions have been noted,
usually erythematous in nature. In several instances an
extensive general urticaria has been observed. The respira-
tion is not particularly accelerated, though the pulse is often
rapid and somewhat dicrotic. The lungs are generally clear
on auscultation and percussion, though, not infrequently,
evidences of a general bronchitis—*sonorous* and *sibilant râles*—
might be heard throughout the chest, more frequently in
the back. The heart sounds are usually clear, though a
soft systolic murmur may be heard over the body of the
heart. The abdomen is usually natural in appearance or
distended; as a rule, there is constipation. The area of
hepatic dullness is often somewhat increased. There is
frequently tenderness on pressure in the region of the liver
and spleen, while the area of the splenic dullness is almost
invariably increased. In most cases the spleen is easily
palpable. In fresh cases the border is rounded and soft ; in
older cases, where there have been numerous previous attacks,
the border is often sharp and firm, reaching sometimes a
considerable distance below the costal margin. The splenic
tumour is particularly striking in children. The most marked
splenic enlargements occur, in the cases which show the

more irregular æstivo-autumnal fevers. Mussuriany (St. Petersb. Med Woch, 1884) noted the presence of a soft souffle over the splenic area, which Bouchard has compared to the uterine bruit. The duration of the febrile period is usually four or five hours, though, not infrequently, considerably longer; and during it the temperature reaches its maximum height, thermometric registrations of it as high as 108" F. having been observed.

3rd stage.—The third or *sweating stage* of the paroxysm usually follows quite suddenly after the stage of pyrexia has existed for four or five hours The patient begins to feel relief from the sensation of oppressive heat from which he had been suffering, and then, quite suddenly, breaks into a profuse sweat. The sweating is often excessive; the night clothes and bedding may be soaked. In association with this the temperature falls, usually quite rapidly. The pulse, which has been rapid, becomes slow and full, and the patient often passes into a refreshing sleep. The temperature falls, almost invariably to a sub-normal point The sweating is generally somewhat longer than the rise of temperature, though it may be very short and sudden ; it commonly lasts from two to four hours, though often longer than this. The duration of the sweating stage varies considerably. About 11 hours would represent the average length of the entire paroxysm from the time the temperature passed 99° F. until it reached this point again.

The paroxysms occur more frequently during the day than during the night, the onset perhaps being more commonly noted between midnight and noon, though it may occur at any hour of the day or night : indeed, it is not at all uncommon to find paroxysm beginning in the afternoon. The paroxysm in children is not the same as that seen in adults. Very commonly in young children both the first and the third stages, the chill and the sweating, may be absent, or abortive. The first stage is then generally

represented by a slight restlessness. The face looks pinched, the eyes are sunken, the finger tips and toes become cyanotic and cold, while the child may yawn and stretch itself. Nausea, vomiting, and diarrhœa are particularly common. These may be the only manifestations of the first stage. Commonly, these symptoms are followed by grave nervous phenomena. The chill in malaria, as in other acute diseases, is not infrequently represented in the young child by general convulsions. These begin usually with a slight spasmodic twitching of the eyelids or of the extremities, the spasm soon becoming general. The first and third stage of the paroxysm may be entirely lacking in many instances, leaving out of account a slight coldness of the hands and blueness of the finger-tips, as well as a somewhat pinched expression of the countenance in the first stage.

The patient often feels quite well during the period of intermission, so much so that it is not uncommon for patients to pass through a number of paroxysms before calling in a physician, believing after each that the disease is at an end. The temperature after the sweating stage becomes almost invariably subnormal, and often remains so during the greater part of the next day. About 48 hours after the onset of the first paroxysm, the fresh group of parasites proceeding from the segmentation of two days before having reached maturity and entered again upon segmentation, a fresh paroxysm begins. Sight anticipatory paroxysms are very common, more so than retardation. Often, as has been said, the time of onset of several successive paroxysms is almost exactly the same. More commonly, there are slight variations of an hour or two, anticipation or retardation. In these instances the parasites pass their cycle of existence through a little quicker or a little slower than in the typical 48 hours.

Double infections—*quotidian intermittent fever.*— Among the mildest forms of malarial fever observed in

temperate climates are the single tertian infections ; more commonly the individual shows an infection with two groups of the tertian parasite. These groups reach maturity on alternate days. Segmentation, then, of a group of parasite occurs every day, and, as one might expect, daily paroxysms, quotidian intermittent fever, results therefrom. The paroxysms in these instances are similar in every way to those of single tertian infections. The manner of onset and the durations are the same, while during the periods of intermissions the temperature is likewise always subnormal It is common, however, for the paroxysms on successive days to show slight constant differences in their hours of onset one group of parasites arriving at maturity at an hour slightly different from that of the other. These differences are usually not great, though they may be considerable, one paroxysm beginning in the morning, that upon the following day in the afternoon. Very commonly one set of organism is more numerous than the other, causing thus a more severe paroxysm. The chart then shows alternate mild and severe attacks. Even without the confirmation, obtained by submitting the blood to a special examination, these facts alone might lead to the recognition of the dependence of this quotidian fever upon a double infection.

Quartan fever.—There are three types of quartan fever requiring description, *viz.*, *single infection* or *quartan intermittent* fever ; *double infections* or *double quartan intermittent* fever ; and *triple infections* or *quotidian* (Triple quartan) *intermittent fever.*

Single infections—*quartan intermittent fever.* —This form of malarial fever is due to the presence in the blood of the quartan parasite, an organism which, just as in the case of the tertian parasite, possesses the remarkable characteristic of existing in the blood in great groups, all the members of which are, approximately, at the same stage

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of development. The cycle of development of the quartan parasite lasts approximately seventy-two hours, segmentation occurring every *fourth* day. The characteristics, then, of single quartan infections are quartan intermittent paroxysms two days of complete intermissions existing between. The paroxysm in quartan fever resembles in all its features that observed in tertian infection. The duration in these cases averages between 10 or 11 hours. The same periods of subnormal temperature, lasting often during the greater part of the two days of intermission, are observed. A tendency towards anticipation or retardation in the paroxysm is less often noted than in tertian infection ; and the regularity of the paroxysms in quartan infection is the most remarkable characteristic of the disease.

Double infections—*double quartan fever*.—There may often be present in the blood at the same time more than one group of quartan parasites. When two groups are present, segmentation usually occurs on two successive days, with a day of intermission following. Clinically therefore these double infections are characterised by chills upon two successive days, with a day of complete intermission following. The examination of the blood shows the presence of two groups of the quartan parasite ; and the paroxysms in these instances are exactly similar to those observed in single infection.

Triple infections—*triple quartan fever*.—It is no usual experience to find the three groups of the quartan parasite present in the blood at the same time. These groups reach maturity on successive days, and cause, therefore, quotidian intermittent fever. The symptoms of quotidian fever depending upon a triple quartan infection differ often in no wise from those depending upon a double tertian infection ; and examination of the blood shows in these instances the presence, in different stages of development, of three groups of the quartan parasite. Daily paroxysms,

exactly similar in nature, occur in both instances. The same period of subnormal temperature may be noted, and the diagnosis, without examination of the blood, may be impossible.

Aestivo-autumnal Fever.—The æstivo-autumnal is a type of fever that differs materially from the regular intermittent fevers of the early part of the malarial seasons. It depends upon the presence in the blood of the smaller organism first described by Marchiafava and Celli, the æstivo-autumnal parasite This organism possesses to a much less marked degree the characteristic of existing in large sharply defined groups, while the length of the cycle of existence appears to vary considerably. At the beginning of many infections an arrangement of groups may be made out, and this arrangement may exist for a certain length of time. Usually before the process has lasted very long, organism in different stages of development may be found at any time during the fever. In some instances groups of parasites, with a cycle lasting about 24 hours, have apparently been made out, while in other distinct groups appear to pass through a cycle lasting considerably longer, as long as 48 hours or even more. There are very varied forms of æstivo-autumnal to be met with in practice. Quotidian intermittent fever is not at all an infrequent form. Here the paroxysm may resemble very closely those of tertian or quartan fever, and in some instances, without the examination of the blood the distinction from double tertian or triple quartan infections cannot be made. In these instances the process begins with a sharp chill, and ends with a marked sweating stage, the duration of the paroxysm being perhaps exactly similar to that in the regularly intermittent fevers. More commonly, the paroxysms are longer and more drawn out, lasting perhaps as long as 20 hours. Here the first stage often differs greatly from that in tertian or quartan fever while in the regularly intermittent fevers the onset is

rapid and usually associated with a chill, in these instances the rise may be much more gradual, while the chill is not infrequently altogether lacking. Often a slight transient chill may be observed sometimes after the beginning of the rise in temperature. The chill in æstivo-autumnal fever can by no means be called the initial symptom in the paroxysm ; the fever has often become well marked before the onset of the rigor. Usually, after a certain number of paroxysms, a distinct irregularity in the fever becomes evident. Either from the lengthening out of one of the paroxysms or from the anticipation of the following paroxysm, the intermissions between the two becomes, perhaps, completely obliterated or indicated only by a slight drop in the temperature, until there results an irregular continued fever in which there is no trace of the paroxysms.

Recurrence of the early paroxysm at greater intervals, the one from the other, is not infrequently observed. These intervals are frequently 48 hours, more or less (" æstivo-autumnal tertian fever ; malignant tertian fever." Marchia-fava and Bignami). In these instances the paroxysms are usually particularly long, lasting sometimes as much as 36 hours. The very gradual rise in temperature, which is often unaccompanied by a chill, and the slow fall, are in striking contrast to the chart of an ordinary tertian fever. The authors cited in parenthesis above, who believed that they can distinguish two separate types of the æstivo-autumnal para-sites, the quotidian and the tertian, have described minutely the fever curve in these cases with longer intervals. This class of cases they term " malignant tertian fever," in con-tradistinction to the milder regularly intermittent tertian fever. They describe what they believe to be a characteristic fever curve, the more or less sudden onset of the symptoms, a pseudo-crisis, a precritical elevation of temperature, which often reaches a point higher than has been previously attain-ed, and, finally, the actual crisis. Charts similar to this have

been observed by others, and reproduced in various publications, though they have not seen a sufficient number of instances to justify them in believing that such a curve is characteristic of a particular, separate type of parasite. It is certainly true that irregular oscillations, in the curve of the fever produced by these parasites, are very common. The periods of intermissions between paroxysms show usually a subnormal temperature. As may be readily understood on consideration of the length of the paroxysm—lasting, as it often does, 36 hours or more—the periods of *apyrexia* are very brief.

The irregularity in the hour of onset of the paroxysms is particularly striking in those cases in which the paroxysms occur at intervals of approximately 48 hours one from another. In some cases there is marked retardation, intervals of considerably more than 48 hours occurring between the beginning of one paroxym and that of its successor. More frequently, however, there is an anticipation, the paroxsyms recurring at intervals of less than 48 hours. Now, if, as already stated, the individual paroxysm should last 36 hours or more, it may readily be seen how short the period of intermission in these cases would be. Often, then, there is what is termed " *malignant remittent fever,* " in which we have an almost continuous high temperature, with occasional remissions or intermissions lasting, perhaps, less than 30 minutes.

Either owing to an excessive prolongation of the first paroxysm or to an anticipation of the succeeding one, in many instances the new paroxysm begins before the previous one has finished. In these cases the result is, of course, a " continuous" fever. Usually the continuous fevers result from æstivo-autumnal infections, though the temperature may never reach the normal point, yet it shows indications of the paroxysms, and sometimes occasionally abortive chills. In some instances, all evidence of paroxysms may be absent, the chart closely simulating that of enteric fever. Such cases

are probably often due to infections with more than one group of parasites. The fact that the segmentation of a given group of parasites occurs through an appreciably greater length of time than in regularly intermittent fevers probably accounts for the long duration of some of the paroxysm. So it comes that the chart of æstivo-autumnal fever presents very commonly somewhat the following picture : --

At the onset there are several intermittent paroxysms occurring at intervals of from 24 to 48 hours or a little more. After a few of these attacks the fever becomes irregular or continued. As already stated, this may occur through modifications of the curve in the individual paroxysm, or by the same thing in connection with the succession of the paroxysms. The modifications of the curve that are important are the following: Firstly, the lack of a sharp initial elevation, so that the curve rises in a slow and continuous manner; secondly, the occurrence of a *pseudo-crisis*, so that the attack tends to lose its individuality; and, thirdly, the prolongation of the paroxysm, with which an exaggeration of the thermic oscillations during the fastigium is usually associated. The modifications in the succession of the paroxysms may be : firstly, the reduplication of the attack ; secondly, the anticipation of the paroxysms ; thirdly, the retardation of the paroxysms, by which apyrexia is made incomplete ; and, fourthly, the occurrence of slight oscillations in temperature during the period which ought to be one of apyrexia.

It is a very common thing to find that the case is already one of remittent or continued fever when it comes under observation. The chills are frequently absent ; the patient complains bitterly of headache and pains in his back and limbs. He is usually *dull, drowsy,* and *pathetic,* though there may be marked *delirium.* The face is *flushed,* conjunctivæ are *injected,* tongue red and *coated ;* there is a *sordes* upon the lips and teeth ; the patient remains continu-

ally in a condition similar to that described in the febrile stage of the ordinary paroxysm. In these instances it is often absolutely impossible, without an examination of the blood, to distinguish the case from one of typhoid fever. One repeatedly sees patients with æstivo-autumnal malaria placed under treatment as cases of typhoid fever, the attention being first drawn to the true condition of things by a sudden fall of the temperature to normal, or by the discovery of the small amœboid hyaline parasites within the red corpuscles. Grave cerebral or abdominal symptoms develop, often early in the course of these subcontinuous fevers, which frequently tend to become pernicious. Careful observation may show that these symptoms are paroxysmal. *Delirium, drowsiness, stupor, coma, grave* cerebral symptoms, local *spasms*, general *convulsive seizures* may occur, or perhaps profuse *vomiting* or choleriform *diarrhœa* with *collapse.* In fact, in the course of the subcontinuous æstivo-autumnal infections, any of the symptoms which will be described under the pernicious fevers may suddenly develop.

The term "*Malarial Remittent Fever*" has sometimes been applied to these cases of more or less continued fever. They have been specially studied by Bacelli, who recognised their true malarial nature, under the name of "*subcontinua typhoidea.*" The tendency of the regularly intermittent fevers. when left to themselves, is towards spontaneous recovery after a certain number of paroxysms and, while relapses are common and productive, perhaps, of grave secondary disturbances, anæmia, nephritis, etc., the tendency to become pernicious is rarely observed. This is not true of æstivo-autumnal infections as a class. In many instances, indeed, when placed under hygienic conditions the same tendency towards spontaneous recovery, usually with relapses, is to be observed. Often an untreated infection becomes steadily more aggravated, until, finally, death occurs in the midst of the so-called pernicious symptoms. Again, æstivo-autumnal

infection may be associated, in other cases, with but slight
rise in temperature ; there be no sharp paroxysm, the patients
complaining only of *langour, anorexia, headache,* and *pains*
in the back and extremities. Such cases probably often pass
into the condition known as *chronic* malarial *cachexia* ; and
may lead to errors in diagnosis, though there is usually,
if the case has existed for any length of time, a certain
degree of anæmia, with the characteristic sallow hue of the
skin, while the spleen is always hypertrophied.

Pernicious malarial fevers.—The term "*pernicious*"
has been applied to certain very *malignant* forms of malarial
fevers.   It is quite true that the term "*Malignant fevers*" used
by the translators of Marchiafava and Bignami's work (the
parasites of malarial fevers, New Syd., Soc., London, 1894) is,
in the abstract, better ; but the eradication of the word "*perni-
cious*" appears to the writer injudicious, as it is so firmly
implanted in the general usage.   The disease, almost invari-
ably, depends upon infection with the æstivo-autumnal para-
site.   In temperate climates these pernicious fevers are
rare, but in the tropics they are extremely common.   The per-
nicious nature of an attack depends, generally, upon several
cases : (1) the great numbers of parasites present, and
their capacity for rapid multiplication ; (2) the special in-
volvement of certain vital organs by the parasites, which,
as has already been pointed out, show a remarkable tendency
towards accumulation in certain definite organs, varying in
different cases ; (3) possibly upon greater or less virulence
of the parasite.   The latter statement is based upon the
assumption that the malarial parasites produce a specific toxic
substance.   Certain authors thus believe that, in the case of
infection with a very malignant parasite, pernicious symp-
toms may result, while but a small number of parasites are
present, particularly if the chief seat of development of the
parasite be localised in a particularly vital spot.   This is,
however, doubtful.   While it is probable that a specific toxic

substance may be produced by the parasite, and while there is very good reason to believe that there is a difference between the malignity of the parasites in different instances, yet, in a general way, the severity of the symptoms, as demonstrated long ago by Golgi, appears to depend largely upon the number of parasites present. In a general way it may be definitely stated that pernicious fever never occurs without the presence of a considerable number of parasites, though in the peripheral circulation in some of these instances very few organisms may be discoverable. The conditions through which malarial infection becomes pernicious are : (1) that the infection be produced by one of the varieties of the æstivo-autumnal parasite. On this condition all are agreed, though there are exceptions to this rule, but they are rare— characteristic comatose pernicious fever having been known to be due to a double tertian infection. (2) The second condition relates to the abundance of the parasites, and it may be stated as follows :—In pernicious fevers, if one takes into consideration not only the examination of the blood from the finger, but also the condition in the vessels of the various organs, it is a striking fact that the distribution of the parasites may vary in individual cases, their total number is always considerable. As regards the distribution, one may make the following distinctions. There exist (1) cases in which the number of the parasites is most abundant, while all the organs are uniformly invaded. These are the most common forms of pernicious fever and are usually accompanied by coma. There are some cases in this category in which the number of parasites in the blood of the finger, of the spleen, and of the bone-marrow, etc., is enormous, while the number in the brain is scanty ; clinically, the absence of cerebral phenomena is noted ; (2) cases in which the number of parasites is absolutely and relatively scanty in the bone-marrow, in the spleen, in the liver, while there

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may be relatively few in the blood of the finger, yet other organs are crowded with parasites. Among these the following localisations are to be made out : —(a) The stomach and intestines are chiefly invaded; in these organs the mature forms of the parasite are usually found; these are the cases of pernicious fever in which, clinically intestinal phenomena are to be observed. (b) The brain and meninges are filled with parasites either in sporulation or in all their stages of development; in such cases it is difficult to find not only the sporulating forms, but even young parasites in the spleen. Clinically, there are cerebral phenomena. Though usually several paroxysms have previously existed, the pernicious symptoms may come on quite early in the course of the infection. Almost the first symptoms observed in malarial districts may be of a pernicious character.

Clinical Varieties.

The pernicious fevers present several varieties, all of which merit special description.

Algid form.—In this type of pernicious malaria, after several paroxysms, which are in no way remarkable, the patient very suddenly passes into a condition of extreme collapse. This does not occur at the beginning of the paroxysms, but at a time when the stage of the fever should exist. The temperature may be but slightly elevated : indeed in some instances it is subnormal. The condition is not unlike that of the Asiatic cholera. The mind is clear, there is little suffering, but extreme collapse. The eyes are sunken ; the features drawn and pinched; the face expressionless ; the tongue dry ; the skin moist and covered with cold sweat. The patient may be so quiet and uncomplaining that it may be only through an accidental examination of the pulse that the true state of affairs may be discovered. The pulse is very rapid and feeble and thready, almost impalpable, becoming imperceptible at the wrist before death. The

bdomen is usually retracted ; there is often tenderness on pressure in the region of the liver and spleen ; the latter is palpable. Physical examination of the thorax is negative excepting for the feeble action of the heart. The second sound at the base may be quite inaudible. The course of the disease is sometimes extremely insidious and fatal.

Comatose form.—By far the most frequently observed type of pernicious malaria is that accompanied by *coma;* recovery may result after the gravest symptoms, but the paroxysm is usually followed rapidly by a second, which generally proves fatal, if no treatment is adopted. In the comatose type, in the earlier part of the paroxysm, the patient may be slightly delirious, but he soon becomes drowsy and somnambulent, passing finally into a condition of profound *coma.* Not infrequently, in grave malarious districts, the patient comes for the first time under one's observation while in this condition ; indeed, during the last epidemic year cases of such nature were very numerously observed in this place. He is profoundly *unconscious ;* the respiration is often *stertorous,* and occasionally of the *Cheyne-Stokes,* type. The pupils may be contracted or dilated, sometimes perhaps they are unequal. There is often—not an unimportant point—a slight jaundice. Not infrequently there is *hiccough ;* the pulse may be full, slow, and of high tension, though towards the end it is often rapid, irregular, and feeble. Local spasms of certain muscles may occur. Thus there may be well-marked spasm of the lower facial muscles on one side, which may disappear with paroxysm.

Delirious form.—Most decided symptoms of a different nature may occur in other cases. Delirium, which may be maniacal, may be observed. Active *delusions* and *halluci- ations* are not uncommon, while in some cases *tetanic convulsions* have been noted. In a number of cases *hemi- plegia* have been associated with the paroxysm, disappearing after the attack. At times distinct symptoms of *bulbar*

paralysis may occur. *Post-mortem* confirmation of the special
localisation of the parasite in certain foci in the medulla can
usually be obtained in these cases.

Hæmorrhagic form.—In certain cases of pernicious
malarial fever grave hæmorrhages may occur. Thus, there
may be punctiform hæmorrhages in the skin, the mucous
membranes, the retina, and the brain, and these may be
manifested in all pernicious fevers. But there is one variety
in which the symptom of the greatest gravity and danger
consists in these hæmorrhages. They are seen not only
in the skin, which may be covered with them, but in the
mucosa of the nose, the bronchi, the intestines, the stomach,
and the genital organs ; and they may be so abundant that
they cause grave anæmia in a few hours, whence arise
the loss of strength, a thready pulse, dulness of the
sensorium, delirium, and convulsions. At the end of the
attack the hæmorrhages also cease, but the consequence of
their occurrence may be such that recourse to all the known
means of treating ordinary acute anæmia may be necessary
to avert a catastrophe. Furthermore, the anæmia secondary
to this form of pernicious fever is of considerable duration,
and is sometimes rebellious to treatment for a long period.
The hæmorrhagic pernicious fevers may be subdivided into
various forms, giving each the name of the predominant
hæmorrhage—*e.g.*, *scorbutic, epistactic, hæmoptic, hæmatemetic,
enterorrhagic, metrorrhagic,* etc.; by no means any of these
is uncommon to come across in tropic. It is interesting to
record that the author had an opportunity of an observation
in ten cases in one year that the old women whose ages
varied from 50 to 70 had their menstrual flow commenced
during an acute attack of fever, and that ceased after
administration of quinine.

Diaphoretic form.—Many writers have described a
diaphoretic or sudoriferous type of paroxysm, in which, during
the last stage, the sweating becomes excessive, and the patient

passes into a condition of collapse with a thready pulse and cold extremities. The case may end fatally if not energetically treated ; for the patient is depressed and groans in anguish, his features are drawn into an expression of painful anxiety, the abdomen is retracted and painful, the tongue red and dry, the pulse thready, and the extremities are very cold.

Bilious form.—The chief symptoms of this type of pernicious fever is the vomiting of large quantities of bile-stained fluid, and this phenomenon is usually accompanied by stools similar to those passed during a bilious attack.

Gastralgic and cardialgic form—Even in the absence of marked intestinal symptoms there may occur severe gastralgic paroxysms with profuse vomiting, and often with hæmatemesis. In other cases there may be a syncopal attack in which the patient presents symptoms of grave collapse, the severe cardiac disturbance requiring prompt measures for its relief.

Choleriform form.—The patient may present a picture resembling strongly that of Asiatic cholera in certain cases in which the chief localisation of the parasite is in the stomach and intestines. These cases have been particularly studied by Marchiafava (Centralbl. f. Allg. Path. u. Anat., 1894, v. No 10, 418) The paroxysm usually begins with profuse vomiting and diarrhœa: the discharges may resemble those of cholera. The skin is cold, moist, and clammy. There is cyanosis of the lips, and extremities ; the pulse is rapid and thread-like. There may be cramps in the extremities. The condition closely resembles the *algid* stages of Asiatic cholera. If the paroxysm be not fatal, profuse sweating may follow, with an intermission in the symptoms. Post-mortem, the mucous membrane, may in the stomach and intestines be found filled with malarial parasites, and actual thrombosis of the vessels of the mucous membrane, with superficial necrosis and ulceration, may be produced by the latter.

Pneumonic or dyspnœic form.—A type of paroxysm the symptoms of which are strongly suggestive of pneumonia, has been described by Bacelli (Studien Uber Malaria, Berlin, 1895) and others. Bacelli, as long ago as 1866, recognised this condition to be distinct from a true complicating pneumonia. It is certainly not an inflammation of the lungs, it is more probably an active congestion of the pulmonary vessels, and due to the capillaries of the lungs being the seat of a special localisation of the parasite of the disease. There is intense thoracic pain, great dyspnœa, and a painful cough. There may be moderate dulness over the affected lung with *coarse, sonorous,* and *sibilant* râles, as well as finer *moist* ones. Laveran has seen a fairly abundant hæmoptysis following an acute dyspnœic paroxysm. In other instances— despite the extreme dyspnœa, physical examination may be quite negative. The sputum is mixed with dark fluid and clotted blood.

Hæmoglobinuric form.—Many authors assign to this type of the disease a special chapter under the heading of "*Malarial Hæmaturia,*" for the affection is of great interest and clinical importance. In the grave fevers of certain malarious districts *hæmoglobinuria* is not an uncommon symptom ; but in temperate climates it is very seldom seen. The ultimate cause of its production is still in dispute. A continual destruction of the red blood corpuscles is going on throughout every malarial infection. This occurs in various ways :—(1) The parasites, developing within the corpuscles, form the *black pigment, melanin,* at the expense of the corpuscles in which they grow, corpuscles becoming gradually discolourised and destroyed. (2) In many instances the red blood corpuscles containing the parasite undergo a premature necrosis, becoming brassy-coloured and shrunken. (3) Sometimes the decolourisation of the corpuscles containing the parasite occurs quite suddenly, the corpuscles bursting, as it were, and setting free their *hæmoglobin* in the blood stream.

Thus, during an ordinary malarial attack, there is always a certain amount of hæmoglobin set free in the serum ; but, as this amount does not pass beyond the limit of the quantity which can be disposed of by the liver, it does not appear in the urine. It is doubtless, in part, this constant destruction of the red corpuscles, with the liberation of their hæmoglobin, to which the *polycholia* and slight jaundice, so commonly observed in malaria, are due. Ponfick estimates that up to one-sixth the total number of the red blood corpuscles may be destroyed and disposed of in the economy without the hæmoglobin appearing, as *such*, in the urine. If this destruction of the red blood corpuscles becomes unusually great, and the quantity of hæmoglobin separated from the discoplasma of the red blood corpuscles exceeds the amount which can be taken care of by the liver, hæmoglobinuria will result. It is not only the infected corpuscles which lose their hæmoglobin in these instances. Great numbers of their uninfected neighbours are equally affected, just as in the ordinary paroxysmal hæmoglobinuria. Some substance, exclusively toxic to the discoplasma of the red blood-corpuscles must be present in the circulation, or some change has taken place in the blood serum by which it has lost its *isotonicity ;* but what these changes are, and to what they are due, are by no means clear. There is much which might lead us to believe with Bacelli that some toxic substance produced perhaps by the parasite itself, may be responsible for these phenomena. In the present state of our knowledge it is difficult to understand why hæmoglobinuria should be so common in certain regions—West Africa, Greece and India for example—and so infrequent in many other malarious localities. As far as the experience of author concerns with regard to India which has peculiar surroundings and circumstances for the occurrence of this affection, will be dealt later on.

Cases of this type must be regarded as among the severest manifestations of malarial fever. The same condi-

tion is known in West Africa as "*Black-water fever.*" By many observers, particularly by the French, the term "*Bilious hæmoglobinuric fever*" has been used. Not infrequently the term "hæmaturic" is used, and, indeed, as the interesting researches of Joseph Jones show, actual hæmaturia often occurs. The hæmoglobinuric attack is rarely the initial symptom of the infection. Usually the patient has had repeated attacks of malaria, the *hæoglobinuria* appearing suddenly with the relapse, or, if it be the first infection, the *hæmoglobinuric* attack is preceded by several intermittent paroxysms. In cases where either in a relapse or in a primary infection the *hæmoglobinuria* appears with the first actual paroxysm, there are often prodromal symptoms lasting for from several hours to sometimes several days. It is probable that these are associated with moderate fever, and often represent abortive paroxysms. There is loss of appetite, headache, indefinite pains in the extremities and the back. It should be remembered that in many paroxysms of the more ordinary types of æstivo-autumnal fever the gradual onset of the paroxysm without chill is frequent: this is not true in the case of the *hæmoglobinuric* paroxysm, which begins almost invariably with a severe shaking chill. This is followed by an intense pain in the back, the head and the extremities, and by profuse vomiting ; the vomits consist of a deeply bile-stained fluid. The face is flushed, the conjunctivæ are injected ; the pulse is rapid ; and the patient is usually in a condition of grave anxiety and apprehension. Profuse diarrhœa or one or two loose motions a day is generally present ; and the skin is usually markedly icteric in hue.

Somewhat reddish colour of the urine is noticed in connection with the early stage of the paroxysm. This hue rapidly becomes deeper, and is finally an intense reddish-black colour with something of a greenish tinge, and a greenish-yellow on shaking. The vomitus becomes of a deeper colour—at first yellow, then green, and finally some-

times almost black. The fever is often high, the temperature reaching 106° F., or even higher, in certain cases. There may be frequent calls for motion, the dejecta being green or black in colour, while in other instances there is constipation. During the stage of fever the patient generally becomes jaundiced. There is usually little delirium, the patient being quite conscious and in a condition of great anxiety and agitation. He often complains of severe epigastric pain, which is possibly associated with repeated vomiting ; in other instances, the pains in the loins may be extremely severe, bearing, possibly, some relation to the intense renal congestion.

At the advancement of the disease the urine is of a deep reddish-black colour, and deposits on standing an abundance of a *whitish-grey sediment.* The amount varies considerably in different cases, in some being extremely scanty, in others amounting to as much as one thousand or fifteen hundred cubic centimetres. The specific gravity varies inversely to the amount of urine passed. As the amount is generally somewhat reduced, the specific gravity averages above normal The reaction varies ; it is generally feebly acid. There is usually presence of albumen. But it is not always in all the cases. The writer collected urine of 20 cases of *hæmoglobinuric* fever in a single month and in nine of them albumen was abundantly present ; and in four cases a trace was noticed, and in the rest albumen was wanting. In some instances a test for the biliary colouring matters may be obtained. Kelsch and Kièner assert that this is the rule at the height of the process, while Plehn (Deut. Med. Woch. 1895, Nos. 25, 26, 27), was unable to obtain this test in 8 cases. The sediment consists of *mucus, vesical epithelium,* numerous *granules* and masses of *pigment, renal epithelial* cells, and, almost invariably, *hyaline* and *granular casts* with epithelial cells adherent thereto. In many instances blood corpuscles may also be found, actual hæmorrhages taking place into the kidneys. Often, the

condition is a hæmoglobinuria pure and simple, not a sign of red corpuscle—besides the profuse sediment of a brownish granular material, occasional epithelial cells, and casts— being discoverable on the closest investigation.

Excepting for a slight trace of albumen with occasional casts, the urine, in the simplest and mildest attacks, clears up, and at the same time the temperature remains elevated nine or ten hours and then falls quite suddenly to normal. In some instances a paroxysm of this nature is the last manifestation of the process, and complete recovery follows. In other instances there may be repeated intermittent hæmoglobinuric paroxysms, ending perhaps in recovery. Very frequently, the condition is more severe. The fever lasts much longer ; the vomiting and diarrhœa continue ; the jaundice becomes more intense ; there are perhaps occasional slight intermissions, but in the main the attack is continuous. The urine, as well as the fever, may show occasional temporary changes for the better, but these are of short duration, fresh attacks rapidly follow. In some cases recovery may occur when the patient is apparently on the point of death ; but more often the urine becomes scanty and more albuminous— the patient becomes emaciated and pale, the eyes are sunken, the tongue is dry, the pulse is rapid and feeble, the extreme coldness of the surface of the body in such cases causes collapse and eventually a fatal result follows.

One sometimes comes across cases that run an extremely rapid fatal course. The initial chill, fever, vomiting and diarrhœa are associated with almost complete *suppression* of urine ; that which is passed, often but a few drops, is intensely bloody. There is great agitation, intense prostration, the patient falling into a condition of profound *syncope, coma* and death within a day. Nephritis almost invariably follows the hæmoglobinuric attack. In the milder cases it is transient and slight. In many more severe cases, however, the end of the paroxysms is followed by the symptoms of a well-marked

nephritis, lasting sometimes for weeks and possibly even for months. In a certain number of instances this condition pursues a rapidly fatal course. The albuminuria and casts persist ; the quantity of urine remains steadily below normal ; the patient becomes *uræmic* ; and the patient dies in the midst of delirium or coma or convulsions. There are some malarious regions in which there is no malarial hæmoglobinuria. In some regions where *pernicious* fevers are relatively common, hæmoglobinuria is rarely seen. The cause for this is not very clear. In Rome, for instance, the disease is seldom seen. In certain parts of Africa, on the other hand, it is seen in its most fatal forms, and in Greece it is unusually common. It is not very frequent in most of the malarious districts of the United States of America.

The condition of the blood has already been referred to ; it generally shows the æstivo-autumnal parasite. Predisposing causes appear to be any over-exertion or exposure, and neglect of proper treatment in early stage of malarial paroxysm, indeed, anything which reduces the vitality of the individual. Extremely interesting is the widespread idea in certain regions that quinine, which has so specific an action upon the parasite, may yet have an unfavourable influence, indeed, be the determining cause of the hæmogobinuric paroxysms. In Joseph Jones's very interesting memoirs (Med. and Surg. Memoirs, Vol. II, 1887), a number of assertions of this nature appear. More recently, Plehn in an instructive article upon the black-water fever of Cameroon records his belief that in that climate, at least, the development of hæmoglobinuria is often brought about by the administration of quinine ; while the records of his cases of hæmoglobinuric fever, treated with or without the specific malarial remedy, show that the more favourable course was pursued by those cases which were treated expectantly. This view, however, is not held by the majority of observers. In many of these cases the tendency towards spontaneous

recovery suggests, certainly, that the life of the parasite may be injuriously affected by the presence of the hæmoglobinuria. This subject will be discussed again in connection with the treatment of liver complaints at the end of the chapters.

Scarlatiniform form.—The appearance during a malarial attack of certain cutaneous eruptions, as herpes, and specially urticaria, is very apt to be observed; but these are of no significance, and rapidly subside. The same, however, cannot be said of the diffuse scarlatiniform rash in cases of grave malaria. This form of pernicious fever was observed by the earlier physicians. Morton noted grave fevers with an eruption like that of scarlatina. Others have described cases of malarial infection in which a rash of that nature covered the whole body, and presented also erythema of the fauces, the erythema returning after desquamation in large scales had already lasted for three days. During the eruption the examination of the blood shows the presence of numerous æstivo-autumnal parasites. A typhoid condition followed the second eruption, accompanied by grave icterous and diarrhœa, the patient becoming progressively more anæmic. The parasites in the blood gradually diminish in number. The autopsy in these cases revealed the presence of areas of necrosis in the liver resulting into emboli of hepatic cells in the suprahepatic veins, in addition to the lesions of malaria. This relapsing scarlatiniform erythema in malarial infection recalls those rare cases of the same eruption which have been described as occurring after certain infections., e.g., typhoid fever and pneumonia, and specially acute articular rheumatism.

Condition of the blood in æstivo-autumnal fevers.— This has already been considered in a previous section, when we saw that only the earlier forms of the parasite in its cycle of development were generally found in the peripheral circulation. These are the ring-like or amœboid hyaline bodies, which are often quite free from pigment. As the later

stages in the development of the organism are rarely found in the peripheral circulation, it is natural that the period shortly before and during the early part of the paroxysm should be that in which the smallest number of parasites is to be found on clinical examination of the blood ; and this is actually the case. There are cases of æstivo-autumnal fever where, at this period, a prolonged search must be made before parasites are to be found. They are always present, after the lapse of a few hours. Indeed, after a careful investigation it is probable that there are no dangerous forms of malaria in which the parasite will not be discoverable. One usually observes the *crescentic* and ovoid *pigmented* forms of the organism after the disease has lasted for a week or two. Phagocytosis is very commonly to be noted and the pigment-bearing leucocytes are to be found throughout almost all the periods of the fever. The periodicity in the phagocytic action is much less marked than in the ordinary intermittent fevers. This is due in part to the presence at all times of the parasites in different stages of development, and in part to the early necrosis of the red blood corpuscles which is so common in these fevers, the dead fragments being speedily engulfed and carried away by the colourless elements. Occasionally true macrophages, such as are seen in the spleen, may be found in the peripheral circulation ; these may be enormous, ten times the size of an ordinary leucocytes. They sometimes contain coarse granules, much larger than any ordinarily seen in the blood, having somewhat the appearance of *eosinophile* granules. Entire smaller phagocytes with their included pigment or parasite or corpuscles, red corpuscles,—usually shrunken and brassy-coloured, including a parasite, and the parasite may be contained in these cells.

Malarial fevers with long intermissions.—Besides the ordinary *quotodian, tertian* and *quartan* intermittent fevers, there have been described, from the earliest times, other fevers with intermissions considerably longer ; thus, fevers

with intervals of five, six, seven, eight, nine, ten, eleven, and twelve days, or even longer, have been believed to exist. The observation of fevers with longer intervals, admittedly rare, was made by Celsus, who distinguished, *quotidian*, *tertian* and *quartan* fevers. It is but natural that—consequent upon Golgi's first researches concerning the life-history of the quartan and tertian parasites and after the fact that a third parasite existed, whose cycle, under some circumstances, lasted but twenty-four hours, the fever in every instance being definitely concerned with the segmentation of a group of parasites, many observers have suspected the existence of other varieties of parasites which in turn may be related to these rare fevers with longer intervals. In 1889, Golgi (Ziegler's Beitr., 1890, vii, 647) advanced the hypothesis that the crescent bodies, which we know to be connected with the æstivo-autumnal parasite, might bear a definite relation to these forms of fever. He believed that they represented a form of parasite which underwent a long and slow development, lasting from seven to twelve days; that, finally, segmentation of the crescent forms occurred and paroxysms followed, just as in the case of regularly intermittent fevers. This variety of parasite differed in length of time and the irregularity of the cycle of development, while the paroxysm, in like manner, recurred at irregular intervals, from seven to twelve days apart, or even more. Antolessi and Angelini (Riforma Med., 1890, 320, 326, 332) believed that fevers with longer intervals were associated with this variety of parasite. Canalis (Fortschr. d. Med., 1890, Nos. 8 and 9) held that the æstivo-autumnal parasite also possessed two separate cycles—a shorter, lasting from one to two days, and a longer, associated with the crescent and ovoid bodies, lasting an indefinite length of time, three or four days at least. It is very seldom that one observes clinically cases showing a regular recurrence of paroxysms at intervals longer than every fourth day. On

the other hand, it is not so very unusual to meet with cases where a number of paroxysms have recurred at intervals of, approximately, six to fourteen days. In all these instances one is generally compelled to depend largely upon the statements of the patient. An analysis of those cases which have been observed since the recognition of the parasites and its different varieties shows that these fevers with long intervals may be associated with any of the varieties of parasite which we know. Golgi noted the existence of such paroxysms in patients whose blood showed the æstivo-autumnal parasite. Bignami (Reforma Med., 1891, No. 165, p. 169) and Pes (*ibid.*, 1893, Vol. ii, p. 759) described such cases occurring in connection with the tertian parasite ; while the fact that they may be associated with the presence of any of the varieties of parasites which we know, alone or in combination, has been demonstrated by Vincemzi (Bull. R. Acc. Med. di Roma., 1891-92, p. 631, Arch. per. le Sc. Med., Vol. xix. F. 3, p 263). Bignami appears to have been the first to narrate how these fevers may arise. As stated in the description of the parasite, the mere presence of the organism in the circulating blood is not sufficient to produce subjective symptoms. These appear first only when, from steady multiplication, the number of parasites contained in the circulation has reached a certain necessary quantity. With every period of segmentation their number appreciably increases. Not every fresh segment continues to develop. Were this the case, every infection would become pernicious within a short period. With each paroxysm a very considerable number of young parasites is destroyed—so great a number, in fact, that many (indeed the majority) cases of tertian and quartan fever tend towards spontaneous recovery, though, to be sure, relapses often occur. To what this destruction is due is as yet a matter of doubt. How far it may depend upon the protective power of the blood serum, or upon an active

defensive phagocytosis on the part of the leucocytes, or, possibly, upon the deleterious effects of some toxic substance produced, perhaps by the parasite itself at the time of segmentation, is as yet largely a matter of speculation. It is not an infrequent occurrence to see, more particularly in tertian or quartan infections, a severe paroxysm followed by a complete disappearance of the symptoms, while the blood shows a disappearance of the group of parasites. In such instances, through some means, or other, the greater part, or an entire group of parasites, is destroyed at the time of segmentation. In these cases the result is usually complete apyrexia for a certain length of time from several days to two weeks or even more, and then, after, perhaps, a little warning, a repetition of the paroxysms. In certain cases the first paroxysm may be followed by a period of apyrexia, lasting perhaps eight days before the development of a second febrile attack, and that, in turn, by another intermission of approximately the same length of time, and so on, the chart thus showing an intermittent fever with intervals of, perhaps, eight, or ten or twelve days. Nevertheless, the characteristic parasites of tertian or of quartan fever are revealed by an examination of the blood. From all this it is evident, then, that the explanation of these fevers with long intervals is not to be found in a parasite whose cycle of development lasts an uncommonly great length of time, but in the fact that the first sharp paroxysm is followed by the destruction of so great a number of the parasites that a long period sometimes practically that of the period of incubation of the disease must be passed through before the group again reaches a size sufficient to produce symptoms. The recurrent attacks represent recrudescences from attacks from which recovery has not taken place. Single paroxysm with long intervals, or, more commonly, one of the two paroxysms occurring together with long intervals between them may exist for a very

considerable length of time, in tertian or quartan infections. The imperfect method of treating malarial fever may in another class of cases be responsible for the occurrence of the paroxysms with long intervals. Many patients living in a malarious district are in the habit of taking a large single dose of quinine immediately following any outbreak of fever. For example, a patient may have had paroxysms at intervals of ten days, and the third and fourth one showed the characteristic parasites in the blood. In this instance the patient, by taking a single dose of quinine after each paroxysm, accomplishes the same end which nature accomplishes in the other class of cases, namely, the destruction of the greater part of the group of parasites, a relapse occurring about ten days after the previous attack. The same explanation is probably true in the cases occurring in æstivo-autumnal infections. There is no evidence to show that there is any such thing as a regular type of fever occurring at intervals longer than every fourth day. According to the variety of infection, the paroxysms in these cases differ in no way from those in æstivo-autumnal tertian, or quartan fevers.

Mixed Infections —Though somewhat uncommon, combined infections with one or more varieties of the malarial parasite may occur. Clinically, these cases present usually the features of an ordinary tertian, quartan, or æstivo-autumnal infection ; and without examination of the blood, the presence of the two parasites would often remain unsuspected. This is due to the fact that the two different varieties of the organism are rarely present equal in sufficient number to produce symptoms at the same time. One type of the parasite almost always predominates, and is responsible for the clinical symptoms. Certain cases have been noted where a distinct alternation of symptoms has occurred ; a period of quartan fever, for instance, being followed by a spontaneous recovery, and succeeded by a period of tertian

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fever, which, if untreated, pursues the same course, and gives way finally to a relapse of the quartan infection ; the parasite of both varieties are present at the same time. The common combination is in intemperate climates, at least that of tertian and æstivo-autumnal fever. In rare instances complicated fever curve may arise from a combined infection but this is very uncommon.

Chronic Malaria.—In chronic cases of malarial infection the disease continues in the organs for months or even years. The condition is manifested by febrile attacks which are repeated at greater or lesser intervals, by enlargement of the spleen and liver, and by a secondary anæmic condition and its results. In malarial districts chronic infection is readily recognised by a special earthy complexion, an enlarged abdomen, and torpidity and depression of spirits. Sometimes, in genuine chronic infections, specially if the fever is mild and if the attacks are repeated at long intervals only, the patients may be in good condition, with the exception of a slight and transitory anæmia after the attacks, and may attend to their occupations with their usual activity.

Condition of the urine in malarial fever.—There are no special diagnostic features to be observed in the urine in cases of acute malaria. There are no constant changes in the amount or in the specific gravity of the twenty-four hours' urine. The colour of the urine is somewhat increased, due probably to the increased quantity of the *urobilin* which is derived from the hæmoglobin of the red blood-corpuscles, destroyed by the parasites. The amount of urea excreted during the paroxysms is increased, just as it is during any other acute febrile condition. Albumen is usually present in serious cases, sometimes in about 50 per cent. In many of these instances casts of the renal tubules may be found. Actual nephritis occur, and it may be diffuse or hæmorrhagic in character. Ehrlich's *diazo* reaction may be present in some of the cases. Concerning the increased toxicity of the

urine during malarial fever, some valuable and interesting researches have been made by various observers. Brousse (cited by Laveran, loc., cit. , studying the effects following the injection of the urine of cases of malarial fever into animals, arrived at the following conclusions: " (1) The urotoxic co-efficient calculated by Bouchard's formula, the mean co-efficient being ·464, rises during the paroxysm, and the physiological effects observed are those which usually follow the injection of urine *dyspnœæ myosis*, falling of temperature, exophthalmos, and furthermore convulsions; (2) this toxicity is diminished during the period of convalescence, in intermittent fever, very much below that of the urine during the paroxysm, and, moreover, below that of the normal urine " Investigating the condition of the urine in three cases of malarial fever,—one, a case of tertian fever and two cases of pernicious comatose malaria, — Roque and Lemoine (Rev. de Med., 1890, p. 926) conclude as follows : "(1) The pathogenic agents of paludism form, in the blood, a large quantity of toxic products, a great part of which is eliminated by the urine. This elimination is at its maximum immediately after the paroxysm, and lasts, generally, twenty-four hours, at least in the paroxysms of tertian fever; (2) sulphate of quinine acts by favouring the increase of this elimination ; (3) certain pernicious fevers, showing a complete absence of toxicity in the urine, depend probably upon alterations in the kidneys and liver, and the return of the urinary toxicity should be considered a good prognostic sign; (4) finally, it may be noted that in two cases recovery has followed a more increased elimination of toxins than that observed after the preceding paroxysms." In discussing this paper, Lepine justly remarks that injection should be made not only with the pure urine but also with a solution of the salts of the urine made after calcination ; by which means alone a reliable idea of the toxicity of the urine dependent upon organic compounds can be obtained. While

finding the same general results as Roque, Lemoine, Botazzi
and Pensuti (Lo Sperimentale, Firenze, 1894, xlviii, 232,
254) dispute their conclusions after an elaborate control
research, in ten cases. They collected urine during and
after the febrile periods, and found that during the paroxysm
the urine showed a less intense colour than afterward.
During the febrile periods examination of the urine, with
the ordinary re-agents, which are used in qualitative analysis
showed always a diminished amount of alkaline and earthy
phosphates, while that voided after the paroxysm showed
sometimes a considerable quantity. The specific gravity of
the urine passed after the paroxysm was higher than during
the paroxysm. They state that under other conditions the
urotoxic co-efficient has been shown to run parallel in the
elimination of the potassium salts, while the presence of
peptones in the urine increases appreciably its toxicity.
Both these substances they found present in increased quan-
tities in the urine passed after the paroxysm. The urobilin, as
already stated, is present in increased quantities in the urine
of malarial fever, and specially so in that following the par-
oxysm. The toxicity of this substance has been demonstrated
by these authors, who found that the urine passed after the
paroxysm, when decolourised, lost half its toxicity. They
assert, in opposition to Roque and Lemoine, that there is no
need to suppose the presence of special toxic substances of the
nature of *leucomaines* to account for the toxicity of malarial
urine after the paroxysm ; the potassium, the phosphoric acid,
the peptones, the urinary pigments, and especially urobilin
which are found in this urine in markedly increased quanti-
ties relatively to the normal urine and to that of the febrile
period, are of themselves a sufficient explanation. The
cause of the increased presence of these substances is not
difficult to appreciate. The potassium salts and the pigments,
which they believe to be the chief cause of the hypertoxicity,
result from the destruction of the red blood-corpuscles, and

the phosphoric acid and peptones are doubtless due to dis-
integration and combustion of the albumins and nucleins
of the cellular elements of the tissues. They affirm that they
have been unable to discover any signs of a marked reten-
tion of toxic substances, held by Roque and Lemoine to be
due to disease of the kidneys. They go on to state.
" We think that we have demonstrated (1) that in the malarial
fevers the febrile urine is less toxic than that emitted during
the apyretic stage ; (2) that the urine emitted during the
period of apyrexia is more toxic than normal urine ; (3) that
toxicity of the urine of malarial patients augments constantly
with the succession of febrile attacks, though in some cases
this augmentation appears in the form of unexpected and
irregular exacerbations ; (4) that, as there is nothing specific
in the course of the intoxications produced in rabbits with
malarial urine, there is no need to suppose the presence of
special toxins or substances of the nature of leucomaïnes,
for the salts of potassium, phosphoric acid, the urinary
pigments, the peptones, all of which substances are eli-
minated in increased quantities ; (5) that the injection of
febrile urine is followed by a slower intoxication, charac-
terised by *sopor*, by increased *diuresis*, by *diarrhœa*, and
mydriasis, while the apyretic urine produces a more
acute effect, sometimes fulminating, characterised by clonic
and tonic spasms and myosis, 'exhorbitisms', spastic
expiration ; (6) that to explain this different picture one may
suppose that with febrile urine the *polyuria* and *diarrhœa*
are due chiefly to the increased richness in the urea, while
the peptones may contribute to the production of sopor. In
the febrile urines the salts of potassium, the phosphoric
acid, the urinary pigments, and specially the urobilin,
manifest themselves as substances essentially convulsive,
determine hypertoxicity ; (7) finally, besides the *hæmocytoly-
sis* and the destruction of the cellular elements of the tissues,
and the formation and elimination of toxic substances, there

must exist intermediate factors which account for the absence of increased toxicity after the first febrile paroxysms and the irregular elevation and diminution in the urotoxic co-efficient in some other cases." We may conclude, then that while a distinct increase in the toxicity of the urine has been shown to be present after malarial paroxysms, its dependence upon specific products of the action of the malarial organism has not yet been definitely established.

CHAPTER XV.

SEQUELÆ AND COMPLICATIONS

Regarding the appreciation of the nature of the sequelæ and complications, there is probably no point in the history of development of our knowledge of malarial fevers where so much confusion and misapprehension has existed as in this particular. The relation of the chronic *cachexia* and grave anæmia to malaria has long been recognised, as well as the existence, of an acute post-malarial nephritis. The grave cerebral, nervous, and gastro-intestinal symptoms which may occur with acute malaria have already been referred. Many observers, do even to-day, ascribe to the malarial poison the capacity of producing of itself a considerable number of other complicating processes ordinarily dependent on other specific causes. These observers have in particular described a "*malarial pneumonia*," "*malarial dysentery*," etc. When we consider the many ways in which simple malaria may be complicated or masked, the fact that such misapprehension should have arisen is not remarkable. In this direction the main possibilities are well expressed by Ascoli (Bull. della Soc Lanc. d. Osp. di Roma, An. xii 1891-92, 103) as follows:—" Finally in conclusion, we may distinguish the following clinical forms: (1) Malaria which simulates another pathological process. (2) A disease, the (*ordinary*) course of which is known, which, in an individual suffering with chronic malaria, progresses and develops anomalies in its course according to the stage of the *cachexia*. (3) A fresh malaria develops in a subject who is at the time in an apyretic stage of the disease or suffering from the remains of a former infection (*combinata*). (4) Different varieties of a hæmotozoa exist in the blood of a patient suffering from malaria alone (*mista*). (5) Two febrile

diseases exist together and contemporaneously (*concomitanti*):
(*a*) exerting a reciprocal influence detrimental to the organism
(*proportionate*); in certain of these cases the reciprocal influ-
ence is not manifested throughout the entire course ; (*b*) each
preserving its more constant and common symptomatology
(*associata*). (6) The malaria may prepare the ground for the
development of another acute infection, or it may follow
after another infection has run itself out (*consecutiva*)." For
the purpose of description, we may divide the *sequelæ* and
complications of malarial fever firstly into, those sequelæ or
complications due directly to the changes produced by the
malarial parasites or their toxic products ; and, secondly, into
true complications, and mixed infections.

Regarding the sequelæ and complications due directly
to changes produced by the malarial parasite or their toxic
products, in the section upon the pernicious fevers the acute
symptoms produced by the special localisation of the para-
sites in the brain, lungs, or gastro-intestinal tracts have
already been discussed. To enter into the consideration of
the acute *choreiform* and *comatose* cases, which might so
readily suggest a mixed infection, is therefore quite
unnecessary.

Relapses.—In malarial fever relapses are of very com-
mon occurrence. Indeed, most cases, unless treatment be
thoroughly carried out, show recrudescences in the course
of one or two or three weeks. These are clearly proved to
be due to the fact that all the parasites have not been des-
troyed by the treatment. The few which escape form a
nucleus for the development of new groups, which in the
course of a week or two arrive at a degree of development
sufficient to result in a fresh outbreak of the symptoms,
The recrudescences are, ordinarily, in every way similar to
the original attacks. There is, another variety of relapse
which has been recognised for many years, namely, the
re-appearance of an infection many weeks or months after

all symptoms have disappeared. Undoubtedly, many such cases are fresh infections. There are cases where a fresh infection can be definitely ruled out while the malarial nature of the process is undoubted. There can be little doubt as to the nature of the case, though the absolute proof, the discovery of the parasite, may be wanting. The explanation of these cases is difficult. It is highly improbable that the parasite has remained present in the blood, passing through the ordinary cycle of development, and yet some form of the parasite must exist throughout this time. Bignami suggests some form of the organism may persist in some of the internal organs, possibly within the protoplasm of some of the cellular elements, which perhaps we have not been able to discover, *e.g.*, a non-staining spore.

Malarial cachexia.—The dyscrasia known as chronic malarial *cachexia* is the commonest sequel of malarial fever. It is well known that in malarious districts many patients allow an infection to continue for weeks, months, or perhaps years, without ever attempting a systematic or thorough treatment. Naturally, the result is a serious drain upon the vital resources of the individual. The course of such a case is commonly as follows : The patient has several paroxysms, and takes a few grains of quinine, which are followed by a disappearance of the fever ; or, after a week or so of paroxysms which have been untreated, the fever disappears spontaneously and frequent relapses occur, which are imporperly treated or allowed to take their own course. In some instances of æstivo-autumnal fever a patient may remain for a long time with a slight and irregular fever, no sharp, definite, malarial paroxysms being observed. The first result of a continued process of this nature is the gradual development of an anæmia which usually becomes marked, and is sometimes extremely grave. The patient has a sallow, grayish-yellow colour; the lips and mucous membranes are blanched ; the tongue is often coated ; and there is

frequently œdema of the dependent parts. Sudden motion or exertion is followed by throbbing of the heart, vertigo or fainting. The gait is tottering and unsteady ; and marked general tremor may be observed. The spleen is usually greatly enlarged, sometimes reaching to the right of the median line. Indeed, some of the largest splenic tumours which occur may be seen in these cases. The hepatic flatness is increased in extent ; the border is often palpable, reaching sometimes a considerable distance below the costal margin. Except for the anæmia, the examination of the blood during any febrile stage may be quite negative. More commonly occasional parasites or pigmented leucocytes may be found, while in æstivo-autumnal infections the characteristic *crescentic* or ovoid pigmented bodies are usually to be seen. Chronic *cachexia* may follow any variety of infection. In the majority of instances, it represents an untreated æstivo-autumnal infection, and in these instances the *crescentic* and *ovoid* forms of the parasite may be found. The same condition also frequently follows repeated attacks, even though the individual attack has been actively treated. The tendency towards dropsical transudations is generally decided, and at times may give rise to confusion. Thus, in several instances, there have been observed cases of moderate anæmia with quite marked œdema of the dependent parts, and complete absence of fever, where, owing to an unsatisfactory history and the failure to find parasites in the blood, the true nature of the process was wholly unsuspected until the appearance, within several weeks, of relapse. Gastro-intestinal disturbances are very common in malarial *cachexia ;* and the patient may be reduced to a distressing condition of marasmus, where he is an easy prey to all sorts of complicating infections, through the grave anæmia, with diarrhœa, œdema of the dependent parts, and the enormous splenic tumour sometimes called " ague cake. " Children not uncommonly suffer from chronic malarial cachexia ; and in these patients, owing to

the irregularity of the symptoms, the true nature of the pro-
cess is often unsuspected. It may lead to the most intense
grade of infantile atrophy. The child becomes greatly
emaciated; the sallow, grayish-yellow, parchment-like skin
hangs in folds; and the mucous membranes are blanched.
The spleen is always enormously enlarged. There are occa-
sionally slight febrile attacks, the child becoming cold and
blue, or, perhaps, showing now and then a slight eclamptic
attack. There are persistent gastro-intestinal disturbances,
e.g., vomiting and diarrhœa, as well as, perhaps, diffuse
bronchitis.

Malarial anæmia.—It is a well-known fact, apparent
both from clinical observation and examination of the blood,
that, after every febrile disease of a certain gravity and
duration, there is a diminution in the number of the red
corpuscle; but in no other infection is anæmia produced with
the same rapidity and to the extent as in malaria. This
fact was within the knowledge of physicians for some time
before the discovery of the malarial parasite. The anæmia
may be of various forms. For example, four types of post-
malarial anæmia are distinguished by Bignami and Dionisi
as follows:—(1) Anæmia in which the examination of the
blood shows alterations similar to those observed in ordinary
secondary anæmia, differing from these cases only in that
the leucocytes are diminished in number. These cases often
show well-marked *oligocythæmia;* or *oligochromæmia* rela-
tively greater; more or less *poikilocytosis* nucleated red
corpuscles or *normoblasts.* The leucocytes, as already stated,
are diminished in number, while the relative proportion of
the large mononuclear forms is increased at the expense of
the *polymorphonuclear* cells. A fatal course is pursued by a
few of the cases, without any change in the hæmatological
condition, though the greater number go on to recovery.
(2) Anæmia in which the blood shows changes or alterations
similar to those common in pernicious anæmia, that is

marked *oligocythæmia* ; *oligochromæmia* relatively less marked *poikilocytosis* ; nucleated red corpuscles, for the most part *gigantoblasts;* leucocytes, diminished in number with an increase often in the small mononuclear forms, and a diminution in the *polymorphonuclear* varieties. Patients thus afflicted almost surely die. (3) Anæmia showing the ordinary characteristics of secondary anæmia, excepting for the complete absence of regenerative forms, nucleated red corpuscles. These cases are progressive and fatal ; and, as already stated, no evidence of regenerative activity is to be found in the bone-marrow at the autopsy. (4) In prolonged cases of malarial cachexia chronic secondary anæmias occur, and they are remarkable for the small number of nucleated red corpuscles present and the marked reduction in the number of the leucocytes, particularly of the polymorpho-nuclear variety. A favourable sign, pointing to a rapid regeneration, is to be found in those post-malarial anæmias which do not show after the clearing up of the infections a *leucocytosis* similar to that in ordinary secondary anæmia.

Nephritis.—The intense acute nephritis, which, as described in a previous section, may follow malarial hæmo-globinuria most strikingly brings to one's notice the grave damage which the kidney may suffer in certain acute malarial infections, either from the direct action of some toxin produced by the hæmatozoa or from the presence in the circulation of injurious substance, due indirectly to the action of the parasite. The kidney rarely escapes a certain amount of damage in any severe malarial infection. The nephritis following malarial fever is usually a mild and acute diffuse process similar to that observed in any infectious disease. In some instances, as stated in the section on malarial hæmaturia, the course may be rapid and fatal, in the majority, the prognosis is favourable, and complete recovery occurs. In these instances of malarial nephritis there is nothing absolutely characteristic, clinically or pathologically,

of the process; and in some cases it is possible that the malarial poison may be responsible for a fatal chronic diffused nephritis.

Amyloid degeneration.—An occasional outcome of a malarial attack is amyloid degeneration. Two cases were reported by Frerichs, and the reports of several others appear in the literature of the disease. These cases have followed after a long series of febrile attacks, those which have been carefully studied having been *æstivo-autumnal* or *obstinate quartan* fever. The clinical symptoms are those of nephritis accompanied by an extremely rapid cachexia, ending fatally, as a rule, within several months. The blood in these cases may show the condition first noted by Ehrlich as of grave portent, namely, complete absence of nucleated red corpuscles and *æsinophile* cells, and the reduction in the number of the leucocytes. At the autopsy the marrow of the long bones shows no evidence of an attempt at regeneration, but appears to be entirely fatty.

Gastro-intestinal disease.—A case of extensive atrophy of the gastro-intestinal mucosa, apparently following an acute malaria, has been reported by PENSUTI. Constant diarrhœa followed the attack resulting in great exhaustion and death from broncho-pneumonia in three months. The case cannot, however, be considered as wholly convincing though Bacelli was inclined to believe that the change was directly due to the action of some toxic substance connected with the malarial infection.

Disease of the liver.—We have already seen that the occurrence of a true atrophic cirrhosis of the liver, as a sequel to malarial fever, has been insisted upon by many observers. There are many instances which would lead us to believe that this may, in some instance, occur; but clinically, in temperate climates, such cases are rarely met with. In tropical climates one does meet occasionally with a true atrophic cirrhosis of the liver in which other etiological

factors of importance have not also been present. On the other hand, chronic hepatitis, resulting usually in an increase in the size of the liver, is commonly observed in malarial cachexia and following repeated malarial infections. This subject again will be discussed in connection with the treatment of relapses of fever later on.

Nervous diseases.—In connection with malarial fevers various cerebral paralyses have been described. They are usually transitory, disappearing under treatment, and are probably due to circulatory disturbances induced mechanically by the parasites. They are almost always cortical in nature The central nervous system is more commonly irritative than peripheral in acute malaria. Occasionally there occur symptoms suggestive of involvement of the spinal cord ; and several Italian observers have reported cases wherein the phenomena have strongly suggested of disseminated sclerosis. In all these instances the parasites were found in the circulating blood, and recovery followed by treatment of quinine. In one of Torti's cases (Bull. d. Soc. Lanc. d. Osp. d. Roma, 1891, XI, 217) there was, however, no fever, notwithstanding the presence of active parasites in the blood. In such instances it is easy to conceive that, without examination of the blood, diagnosis would be quite impossible. Da Costa (Internat. Clinics, 1891, iii, 246) has also reported a case of paraplegia with tremor, severe headache, bitemporal *hæmianopsia*, and mental symptoms, where the blood showed the æstivo-autumnal parasites. Recovery occurred under quinine. The cases of the so-called acute ataxia reported by Kahler and Pick (Beiter, z. Path. u. Anat. des central nervous system, Leipzig, 1879) were probably truly malarial. Bastianelli and Bignami (Bull. d R. Acc. Med. di Roma, 1893-94, Anno. XX, p. 221) have reported a case showing symptoms of the so-called electric chorea or *Dubini's* disease. Lesions secondary to the cerebral localisation of the parasites were considered by them responsible for the process. The latter was associated with

the continued fever, the nature of which was not, at first, determined. An examination of the blood later on showed it to be due to an æstivo-autumnal malarial infection ; and recovery occurred in due course under the influence of quinine. Provided that treatment be begun in time, all of these processes coming on with acute malarial fever are essentially favourable in their course. The fever, according to Boinet and Salibert, may be followed by both spinal and cerebral permanent paralysis. Though definite proof of their malarial origin is wanting, cases of peripheral neuritis following malarial fever have been reported. From what we know, however, of the pathogenesis of the disease, we may readily believe that malarial fever may be followed by acute degenerative lesions in the peripheral nerves, in the same way as these occur in connection with other acute infectious diseases, Emboli of the melaniferous leucocytes in the capillaries have been alleged by Poncet to be productive of a *retinitis* and a *retino-choroiditis*. Though, by no means proved, some good observers affirm that there was some predisposing relation between malarial fever and Raynad's disease or symmetrical gangrene. Just as in the case of any acute infection, various mental affections have been seen to follow malarial fever, so there is nothing specially characteristic in these cases. There now remains to be described the second class of cases, namely, that of the true complications and mixed infections occurring in the disease under consideration : which latter, indeed, like any other acute process, is subject to various complications, many of which are a result of mixed infections with other pathogenic agent. As already mentioned, many of the symptoms caused by mixed infections were believed by the older observers to be due directly to the malarial poison. Since their time, with our increased facilities for study and appreciation of these conditions, the dependence of the complication, in the vast majority of instances, upon a true mixed infection has been established,

Respiratory affections.—Well marked pulmonary symptoms, such as dyspnœa, pain, and hæmoptysis, occurring during the paroxysms have been observed in connection with pernicious fevers. These symptoms, dependent probably upon the special localisation of the parasite in the pulmonary capillaries, are to be sharply distinguished from true pneumonia, which may, and not infrequently does, complicate a malarial attack. Again, in certain instances, an ordinary acute pneumonia may present an intermittent fever which simulates quite closely the chart of intermittent malarial fever. These cases may be readily recognised by the absence of the parasites from the circulating blood. Such cases have been described by Wunderlich, Jaccoud, Bertrand, Andrew, Clark, and others, while Ascoli (Bull. d. R. Acc. di Roma, XV, 88-1889, 355) gives an excellent chart. True acute pneumonia and malarial fever may, however, co-exist. In these instances the course of the pneumonia may be but little influenced by the co-existing malarial fever, while in other instances the exacerbations and remissions of temperature may be quite marked. Here the pulmonary process is a genuine croupous pneumonia, due to infections with the *diplococous lanceolatus*, as has been shown by Marchiafava and Guarnieri (Bull. d. R. Acc. Med. d. Roma, 1888-89, XV, 355). Its course is quite uninfluenced by the administration of quinine, and its connection with malarial fever is purely accidental, unless, as it may be in some instances, a preceding malaria has prepared the ground for the pneumococous infection by reducing the vital forces of the individual. Pneumonia occurring in individuals suffering from chronic malarial cachexia appears to pursue an unusually malignant course, owing, doubtless, to the reduced condition of the patient. Retarded resolution and organisation of the exudate are said by Ascoli to be not uncommon in these cases. Broncho-pneumonia is also occasionally observed in association with malaria; but there

is no direct relation of the former to the latter, as the infection is purely of the secondary character. In acute pernicious malaria certain observers have described the occurrence of symptoms suggesting pleural involvement where, on autopsy, nothing was to be found. In other instances pleurisy and malarial fever may co-exist, although there is nothing whatever to show that this pleurisy is not an entirely separate process from the malarial infection, and it is not influenced by the administration of quinine. There is nothing abnormal, besides this, in the clinical or pathological course of such a pleurisy; and these cases are not to be confounded with the pleural exudates which may occur in cachectics.

Cardiac affection.—It is not to be wondered that the heart is also victim to malarial infection. More evidently the marked anæmia accelerates the action of the heart, so it is not infrequent that patients complain of *palpitation*, so much so that wriggling in bed is troublesome and it is observed especially in cachectic cases.

Typhoid fevers.—There has been much discussion regarding the relation between malarial and typhoid fevers, and in certain countries these relations are probably more generally misunderstood than any one in connection with the febrile diseases. Since the discovery of the malarial parasite, with our modern method of diagnosis, there is no reason for the existence of any such confusion at the present day. The great similarity between the symptoms in certain cases of æstivo-autumnal fever with typhoid fever is well known. There is no excuse whatever for the physician who fails to-day to recognise the malarial nature of such a fever after a few day's observation; for, the parasite being always present, the question will be definitely settled by a simple examination of the blood. The term *typho-malarial* fever is one that is known to the profession, everywhere. It was supposed that in malarious districts

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there existed a continued fever which depended upon the combined action of two poisons, that of malaria and that of typhoid fever—true "*proportionate,*" in the sense of the old Italian observers. This fever was supposed to be markedly resistant to quinine, and to betray its malarial nature by the frequency with which rigours occurred. We know to-day, that typho-malarial fever as a distinct entity does not exist. Rigours occurring in the course of typhoid fever are by no means uncommon, but are of themselves wholly insufficient evidence on which to base a diagnosis of malaria. We know, on the other hand, that there exist in certain localities no malarial fevers which resist for more than three or four days the action of quinine. True complications of typhoid fever and malaria may occur, but they are very rare. Typhoid fever may be acquired by a patient suffering from acute or chronic malaria. A fresh malarial infection may break out, or a slumbering infection may come to life again during the course of typhoid fever. But this condition is uncommon, and in no way justified the term typho-malarial fever. There is little doubt that in the enormous majority of cases referred to today as typho-malarial fever, these are cases of typhoid fever, pure and simple. Too much stress cannot be laid on this point, for the groundless assumption that there exists a fever due to the combined action of the typhoid and the malarial poison, pursuing a fairly characteristic course and calling, from its malarial nature, for the continued use of quinine, has exercised in the past, and is perhaps exercising to-day, an extremely injurious influence upon present-day knowledge. The picture in the case of true mixed infection of typhoid and malarial fever may be most varied. In a fresh malarial attack or a relapse break out during the course of typhoid fever, well marked indications of the paroxysms, varying according to the type of parasite present, may be observed, as shown admirably by the charts published by Gilman Thompson (Trans. Ass. Amer. Phys., 1894, 110).

In these instances the blood shows the presence of the para-
sites; these, with the symptoms dependent upon them, dis-
appears immediately after ordinary doses of quinine. On the
other hand, there may almost be an absence of the symptoms
on the part of the malarial parasite, if the typhoid fever
develops in the course of latent or chronic malarial infections.

Intestinal affections.—During acute paroxysms, parti-
cularly in children, the occurrence of diarrhœa is well known.
The changes produced by the malarial parasites in the intes-
tines in certain acute pernicious cases have already been
considered; the acute choreiform pernicious paroxysm is
truly malarial in nature. There is nothing to show that the
more chronic dysenteries and diarrhœas, often associated
with cachexia, are in any way directly connected with the
action of the malarial poison, excepting in so far as this may
have prepared the ground. It is not impossible to conceive
that severe infections might follow directly upon an acute
choreiform attack. There are several cases on record where
the *amœba coli* had been found in the dejecta of patients suf-
fering simultaneously with acute malaria and dysentery. In
all of these instances the intestinal process might well have
been directly ascribed to the malarial poison. It is exceed-
ingly probable that many of these post-malarial intestinal
affections in tropical climates may in reality be due to a mixed
infection with the true protozoa, considering the frequency
with which the *amœba coli* is associated with tropical dysentery.

Tuberculosis.—The direct antagonism of tuberculosis
to malarial fever and the converse has been affirmed by vari-
ous observers, and particularly by Bondin (Treatise on the
Intermittent Fevers, Paris, 1842). This observer points out
that tuberculosis was rare in countries where malaria existed,
and that where tuberculosis was common malaria was rare.
This assumption has exerted some influence on the minds
of many. Experience has shown that it lacks foundation. In
many of the districts where malaria is common, it is true that

tuberculosis is unusual, owing to certain climatic influences, where tuberculosis is more common, malaria, as is well known, is relatively infrequent. In some regions especially, India, we find malarial fever and tuberculosis side by side, intimately associated occurring by no means infrequently in the same patient. Marchiafava (Bull. d. Assoc. Lanc. d. Osp. d. Roma, 1881, Anno. XV., 186), indeed, as well as others, from actual clinical experience are inclined to believe that chronic malaria is not an unimportant predisposing cause to pulmonary tuberculosis. Others, however, affirm the contrary.

Miscellaneous infections.—It is not so rare as is generally supposed, to find *infections with* other pathogenic organism; thus one may observe furunculosis, parotitis, tonsilitis, and acute rheumatism, while, in one case studied by Barker, there was a general infection with the *streptococus pyogenes.* Bacelli has observed cases of exanthematous diseases complicated during the convalescence by characteristic malarial fever, while Antolessi and Laveran testify to the same effect in cases of small-pox.

Sun-stroke.—It is probably not very common to find chronic malarial fever complicated with thermic fever or sunstroke. Bastianelli and Bignami (Bull. d. R. Acc. Med-d. Roma., 1893-94 Anno XX, p. 151) have demonstrated in an interesting manner the frequency with which such cases have in Italy been considered as essentially malarial in nature. The pernicious malarial fevers are particularly common at the hottest season of the year, while the individuals most subjected to malarial infection are also often those who work bareheaded in the fields, exposed directly to the sun's rays. These observers called attention to the fact that a number of instances of what has been considered pernicious comatose malarial fever, has been reported, on autopsy, only cerebral *hyperæmia,* pulmonary *hypostasis,* and slight degenerative changes in other organs were observed. In some of these cases no malarial parasites were to be

found ; in others, perhaps, the evidence of a recent infection with the presence of a small number of active parasites far too few, however, to account under ordinary circumstances for such grave symptoms. Cases of this nature have led some observers to assume that a very small number of para-sites might give rise to severe pernicious symptoms, owing to their excessive malignancy. It is much more probable that the process represents a complication of malarial fever which might occur in an individual with active malarial fever or in one who has recently recovered from an attack. Indeed, it is not impossible that a preceding malarial infection may render the individual more subject to such attacks by reducing his vitality and strength.

Obstetric and surgical malaria.—The occurrence of post-mortem and post-operative malarial fever has often been described ; and it is too common at the present time to ascribe elevations of temperature during the first few days after operation and during the puerperium to malarial fever. Undoubtedly, the reduced condition of the patient during these periods might, and probably does, favour a recrudescence of the latent malarial infection. It is, on the other hand, pro-bable that the majority of instances of supposed post-mortem and post-operative malaria have no connection whatever with true malarial fever, but represents simply a septic infection.

Reproductive organs —It is not unusual to observe the complete suspension of sexual excitability in man and sterility in woman as a sequel to repeated attacks of fever. But regeneration of these powers after entire recovery is the ultimate fate. It has also been noticed in cachectic patients that they complain of nocturnal emission of seminal fluid on the slightest friction to penis, indeed, sometimes it is very troublesome to patients. During an acute paroxysm abortion and stoppage of menses are generally met with.

Malarial manifestation in the eye.—The troubles in the eye due to malarial infection are not a rare occurrence.

The observations were made with this affection and twenty cases of *Corneal ulceration* and ten cases of *Irritis* were collected, and all these cases had responded readily to appropriate anti-malarial treatment in combination with the usuall ocal applications.

CHAPTER XVI.

DIAGNOSIS, CLINICAL EXAMINATION OF BLOOD AND PROGNOSIS.

Regularly intermittent malarial fevers.—It is usu‑ ally a comparatively simple matter to recognise the regularly intermittent, tertian, and quartan fevers. The regular paroxysms with their three stages of *chill, fever* and *sweating* are so characteristic as to leave little doubt in most instances concerning the nature of the process. The anæmia and the enlarged spleen, which are present in the vast majority of instances, are also important from the point of view of differ‑ ential diagnosis. Occasionally some paroxysms are very closely similar to the malarial access which may occur from other infectious causes, and sometimes the regularity with which the individual paroxysms may succeed one another may lead to errors in diagnosis. The paroxysms in malaria differ in certain respects from those occurring in most other acute infections. Thus, the average duration of the malarial paroxysm, if we estimate the course from the time the temper‑ ature passes 99° F., until it again falls below this point, is from 10 to 12 hours, while in other infections the course is often materially shorter. There may be, of course, mild malarial paroxysms which last but for four or six hours, but in these the temperature is correspondingly moderate; one rarely observes in mild malarial fever temperatures of 104°, 105° or 106° F. in a paroxysm lasting as short a time as 6 hours or even less. There are cases on record of septic infec‑ tion in which, for a considerable time, chills closely simulat‑ ing those of malarial fever occurred, while the anæmia and enlarged spleen were also present. The chief difference noted was the marked differences in the length of the paroxysms, which were sometimes as short as four or five hours, the

temperature reaching, perhaps, within this time a point as high as 106° F., the same may be true of the chills which are not so infrequently seen during the course of typhoid fever ; chills caused, doubtless, by auto-intoxications as yet not understood. One is justified in the suspicion that the fever is not malarial in origin whenever the temperature rises as high as 104° F. and the paroxysm lasts no longer than six hours.

Paroxysms, most closely simulating those of malarial fevers may, however, at times occur from other infections. Thus, cases are on record in which there were observed typical quotidian paroxysms lasting from ten to twelve hours, and beginning nearly at the same hour on two successive days, which were considered to be malarial in nature, for which *otitis media acuta* was ultimately discovered to be responsible. But the intermittent fever, *i.e.*, associated with *pulmonary tuberculosis* is most commonly confused with malaria. It is probably no exaggeration to say that the majority of cases of pulmonary tuberculosis arising in the malarial districts, in tropical zones, at some time in their course, are mistaken for malarial fever, on the other hand, cases of chronic malarial fever misrepresent the pulmonary tuberculosis. The fever recur often at fairly regular hours on succeeding days as a rule in some stages earlier or later of pulmonary tuberculosis, while acute chills may occur in malarial cases. It is natural that the patient should ascribe such symptoms to malaria ; there is, however, no excuse to-day for such error on the part of the physician ; for the examination of the lungs, sputum, and blood will determine the diagnosis, and the sallow colour, the anæmia, and the enlarged spleen will serve to distinguish the malarial process from tuberculosis, where, though the face be pale, the lips, and mucous membranes show usually a good colour, while the splenic enlargement is rare.

One may sometimes confuse with malaria the chills which often occur in the course of *gonorrhœa* or those following

atheterisation or the *passing of sounds* into the urethra.
he latter should therefore always be examined, in doubtful
ases. In some cases of grave septicæmia following gonor-
hœa there may be little or no evidence of an actual urethritis.
Iere the examination of the blood will immediately settle the
uestion. In the one instance there is leucocytosis without
malarial parasites ; in the other, a normal or reduced number
f leucocytes with the presence of the malarial parasite. A
ositive diagnosis in all these cases alone can be made by
iaving recourse to an examination of the blood.

Examination of the Blood.

An oil-immersion lens is absolutely necessary for the
atisfactory examination of the blood ; and it goes without
aying that a reliable microscope is also essential. Though
nuch valuable work has been done with dry lenses and
ower powers, it is folly to attempt careful work without
etter means. The simplest and best method of studying
he malarial parasite is the fresh blood at the bedside or
n the consulting room. The steps towards the preparations
f the specimen are quite simple, though certain precautions
nust be rigidly adhered to. The cover-glasses and the
lides must be carefully washed in alcohol in order
o remove all fatty substance ; they should always be
vashed immediately before use. The blood may be taken
rom any part of the patient's body, though the lobe of the
ar is perhaps preferable, inasmuch as it is least sensitive
ind more readily approached than the finger-tip, while a
imaller puncture will draw more blood. The method is also
nore satisfactory than the puncture of the finger, in that the
atient cannot so readily observe the proceeding—a point of
onsiderable importance in nervous patients and children.
he ear is first thoroughly cleaned ; the lobe is then punctured
vith a small knife or lancet. For the most careful proce-
lure it is advisable to wash the ear with soap and water,

and afterwards with alcohol and ether. But, practically, it is often advisable to make as few preparations as possible, and unless the ear or finger be extremely dirty one may proceed at once. A pin or needle will, of course, answer the purpose, but it is as well to remember that a stab made with by a round blunt-pointed instrument is much more painful than that by a sharp-cutting edge, while a considerably deeper stab is required to draw a given quantity of blood. If a very sharp spear-pointed lancet be used and the lobe of the ear taken firmly between the fingers so that the skin is held tense, very slight pressure with the tip of the lancet will cause an incision deep enough for all purposes. This process is almost without pain to the patient, even a sleeping infant may have blood taken from it without awakening by the careful use of this method. The freshly cleaned cover-glass, after the first several drops of blood have been wiped away, is taken in a pair of forceps and allowed to touch the tip of a minute drop of blood. It is then placed immediately upon a perfectly clean slide. It is well, if a third person be present, to allow the slide to be vigorously rubbed with a clean linen cloth just before the application of the cover-glass. The spreading out of a drop of blood will thus be considerably facilitated. If the slide and cover be perfectly clean, the blood will immediately spread out between them, and unless the drop of blood be too large, the corpuscles may be seen lying side by side entirely altered in their main characteristics. The drop of blood which is taken should be very small unless the patient be very anæmic, and care should be taken that the tip of the drop only touch the cover. If the cover be placed rudely against the drop, and pressed perhaps also against the ear, the blood may so far spread out that the process of drying may have begun at the edge of the drop before the glass is laid upon the slide. The specimens will remain in good condition for a considerable length of time, an hour or more

ong enough to be thoroughly examined. If one desire to observe the specimen for a greater length of time, the periphery of the glass may be surrounded by paraffin or vaseline. In this manner we may see the parasites living and in active motion, while the most exquisite examples of *phagocytosis* may be observed. By enclosing the specimen in paraffin or vaseline the preparations may, if handled carefully, be carried from the residence of the patient to the consulting room; but for this purpose dried and stained preparations should be employed.

It is not a difficult thing to stain a specimen : there is an art which is soon acquired by practice. Stained specimens are of especial assistance in the detection of the unpigmented hyaline bodies, particularly the pale tertian forms and those of the æstivo-autumnal parasites. A small drop of blood flowing from the lobe of the ear or the finger-tip is collected upon a perfectly clean cover-glass, which is immediately placed upon another glass. The drop of blood, if the two covers be perfectly cleaned, spreads out immediately between the glasses. The cover-glasses are then drawn apart. If neither glass be lifted or tilted during this process, they will slide apart readily without sticking. If the glasses have remained together so long that they have begun to adhere, one may be sure that the specimen will be no longer perfect. The glasses, thus prepared, are allowed to dry in the air, which they do usually in the course of a few seconds, and may then be preserved for almost an indefinite length of time. To prepare them for staining, the glasses should be heated upon a copper bar, or in a *thermostat* at a temperature of 100° to 120° C. for two hours, according to the method of Ehrlich, or they may be placed, according to the method of Nikiforov, for two hours in absolute alcohol and ether. Most of the basic aniline nuclear dyes stain the malarial parasite readily. The simplest method is to stain with a concentrated aqueous solution of methylene

blue or Loffler's blue, which consists of 30 c.c. of a con-
centrated alcoholic solution of methylene blue and 100 c c of
a solution (1 : 10,000) of caustic potash. The specimens in
either instance should be stained from thirty seconds to
a minute, washed in water, dried between filter papers, and
mounted in oil or balsam. The nuclei of the leucocytes and
parasites will be stained a clear blue, while the red corpus-
cles will be unstained. The following method should be
employed in order to obtain a contrast stain : the cover-
glass specimen, after fixing in absolute alcohol and ether
from four to twenty-four hours, is placed for a few seconds—
thirty seconds to five minutes—in a 0·5 per cent. solution of
eosin in 60 per cent. alcohol, washed in water, dried between
filter papers, and placed for from thirty seconds to two
minutes in a concentrated aqueous solution of methylene
blue, or in Loffler's methylene blue, washed in water, and
dried between filter papers, and mounted in Canada Balsam.
A *blue* colour given to the nuclei of the leucocytes and para-
sites, while the red corpuscles and œsinophile granules are
stained by the eosin.

A modification of Romanowsky's method gives very
satisfactory results. Two solutions are necessary—a satur-
ated aqueous solution of methylene blue and one per cent.
watery solution of eosin. The older the methylene blue
solution, the better the results. The staining mixture
should be made just before it is to be used. To one
part of the filtered methylene blue solution about two parts
of the eosin solution are added. This is carefully stirred
with a glass rod and poured into a watch-glass ; it should
not be filtered after the mixture has been made. The cover-
glasses, fixed according to the methods above described, or
hardened in alcohol for ten or more minutes, are allowed
to float upon the top of this fluid. The specimens are
covered with another inverted glass, and the whole by
an inverted cylinder which is moistened on the outside.

Good specimens are obtained in from half-an-hour to three hours, best in two or three hours. The simple stain with methylene blue is perfectly satisfactory for rapid work in the consulting room, though sufficient experience, of course, to be able to distinguish precipitates which may be present in the staining solution from parasites that must be observed by the observer. Though the results are uncertain, the experienced observer may obtain sufficiently good specimens for diagnosis in many instances by rapid heating of the cover-glass over the flame for a few minutes.

A positive sign of the malarial nature of the disease is, of course, the finding of the malarial parasites, in the red blood corpuscles. In some instances where the parasites may be very scanty or absent, the presence or absence of a leucocytosis is an important diagnostic sign. As already mentioned, the leucocytes in malarial fever are normal or diminished in number, whereas in almost all processes with which the acute intermittent malarial fever may be confounded there is a well marked leucocytosis. This is the case in all the septic infections which are most likely to be confounded with tertian and quartan fevers; it is also true of tuberculosis, at least, when accompanied by intermittent fever. The presence of a marked leucocytosis is strongly presumptive evidence against the existence of malarial fever. In some instances, where very few parasites are present, the finding of pigment bearing leucocytes may be an important aid in diagnosis. The examination of the blood will determine the diagnosis, while well marked remissions and almost invariably actual intermissions usually occur. Between tertian and quartan infections the differential diagnosis may readily be made in the fresh specimen, less distinctly in the stained. The larger and more actively amœboid, pale tertian parasite with fine brownish, actively dancing pigment granules may be readily distinguished from the smaller, less active, more refractive quartan parasite with its coarser,

more slowly moving, and darker granules. In the case of the tertian parasite the red corpuscles may be seen to become expanded and pale with the growth of the organism, while in the quartan parasite the corpuscles are shrunken and of a deeper, more brassy colour. If the blood be examined just before or during the paroxysm, the more irregularly segmenting tertian organisms, with their numerous—twelve to thirty—segments, may be clearly distinguished from the smaller regular forms in quartan fever with their fever—six to twelve segments. In either instance one may usually readily determine the presence of one or more groups of parasites. As a rule, one may also easily make out combined infections with quartan and tertian parasites, which, though very rare, do exist in certain cases. One should be able to make a differential diagnosis in the stained specimen by observing the size of the pigment and the parasite, as well as the behaviour of the red corpuscle, pale in one instance, taking a deep eosin stain in the other, and the characteristic of the segmenting forms. The *therapeutic test* is usually sufficient if it be impossible to make a microscopical examination of the blood ; thus, in the regularly intermittent fever, there is rarely any recurrence of the fever after 48 hours from the beginning of the administration of quinine ; here in India there are no signs of the fever to be found after the lapse of 24 hours in the case of tertian infection.

Aestivo-autumnal fevers.—The more irregular æstivo-autumnal malarial fevers are not nearly so easy to recognise as the regularly intermittent tertian and quartan fevers. In some instances, where the paroxysms are of shorter duration and occur at regular intervals, usually quotidian, the diagnosis may be as self-evident as in the regularly intermittent fevers. The longer paroxysms, occurring approximately at intervals of 48 hours one from another, with their less rapid rise, but with complete inter-

missions between them, are also generally easily recognised when we take into consideration the anæmia, the enlarged spleen, and the herpes labialis which may be present. When, however, from any of the various causes above-mentioned, separate paroxysms become more or less complicated or merged óne with another, so that at first but slight transient intermission, then perhaps only irregular remissions, and finally a continued fever of some height, result, the diagnosis often more difficult. Such a case often presents itself in the form termed by Baselli " *Subcontinua Typhoidea.*" The general clinical appearances are so similar to those of *typhoid fever* that a distinction without examination of the blood may be quite impossible. In a certain number of instances vestiges of the paroxysms may still be made out, a well marked *acme* in the fever being reached at approximately the same hour at quotidian or tertian intervals, though in other instances all traces of the individual paroxysms may have disappeared. Sometimes the history of several sharply intermittent paroxysms in the beginning of the illness may lead us to a correct diagnosis. Again, the prodormal symptoms are much less frequent and severe, as a rule, in malaria than in typhoid. Delirium may appear quite early in a malarial attack : it is rare during the first few days of a typhoid. Bronchitis is more common in continued malarial fever than in typhoid. Marked abdominal symptoms, though they may occur, are unusual in malaria ; as a rule, in typhoid. Certain erythemata, and especially urticaria, may be present in malarial fever, while the characteristic typhoid roseola does occur. In both instances the spleen is usually enlarged. An important diagnostic sign is the anæmia which is almost invariably present in the malarial fever which has lasted more than a few days, while in typhoid fever anæmia during the first two weeks is rare. In typhoid fever Ehrlich's *diazo* reaction is almost invariably present, while it is not usually found in the urine

of malarial patients. Another important sign is the slight icteric hue which is usually present in malaria, but rarely so in typhoid fever. The examination of the blood here, as in all forms of malarial fever, will clear up any doubt existing ; for the small, amœboid and ring-shaped, hyaline æstivo-autumnal parasites will be found. If the process has lasted a week or more, the pigmented, ovoid and crescentic bodies are also usually present. In rare instances quite severe febrile symptoms may be present, while the peripheral circulation may at times show but a small number of parasites. Here the discovery of pigment bearing leucocytes may often be of assistance. The diminished number of leucocytes which one finds under these circumstances does not help us in the differential diagnosis from typhoid fever, where also the leucocytes are almost invariably subnormal in number. If the case occur in a neighbourhood where it is impossible to obtain the aid of the microscope, the diagnosis may be definitely made by the therapeutic test. No malarial fever, not known, resists good doses of quinine for more than three or four days. In general, if the process be malarial, the temperature will be practically normal by the fourth day. If the process be either non-malarial or a mixed infection, then the drug fails to influence the fever.

The examination of the blood will also serve to distinguish malaria from *typhus fever ;* and the same is the case like-wise with *tuberculosis* or other *septic infections.*

Pernicious malarial fevers.—It is not always easy to effect a correct diagnosis in some of the pernicious forms of malaria. Comatose pernicious fever must be distinguished from sunstroke, plague, uræmia, and other cerebral hæmorrhage. The differentiation of such an attack from sunstroke is by no means simple. Individuals who are subjected to malarial infections are often those working in the fields and most exposed to the rays of the sun of the hottest

season of the year, while the clinical symptoms of the two processes may be closely similar. It is interesting to note that some of the cases recorded of comatose pernicious fever, occurring in infection, tertian were at first mistaken for sunstroke   The slight jaundice, the anæmia, the enlarged spleen, would serve to suggest the malarial nature of the process, while the examination of the blood gives a positive clue to the diagnosis. The same also obtains in the case of the tetanic, the meningeal, the eclamptic, and the hemiplegic types of the disease. In the case of the algid types of paroxysms, where the temperature may be normal or subnormal, and where often from the actual condensation of the blood,— the anæmia may not be as apparent, the diagnosis may be considerably in doubt. Here, icteric and splenic enlargement are suggestive, while examination of the blood which must never be neglected in any case, will give positive diagnosis. The diagnosis in some of the instances of the hæmorrhagic type must be made between malaria and yellow fever. The spleen is often but little enlarged in this affection, and the early appearance of albumin and casts in yellow fever is suggestive of the nature of the disease. The only reliable method of distinction, however, is the examination of the blood. The diagnosis in malarial hæmoglobinuria lies usually between yellow fever, the ordinary paroxysmal hæmoglobinuria, and acute nephritis from some other toxic origin. Examination of the blood must here again be relied upon for a positive diagonsis. A diagonsis of post-partum and post-operative malaria can only be made by an examination of the blood. The blood, apart from the presence of the specific parasites and pigments, shows in the one instance diminution in the number of leucocytes, and well-marked leucocytosis in the other. Furthermore, the malarial paroxysm differ from the paroxysm due to septic infection chiefly by their greater regularity and by their average longer duration. It is usually a comparatively easy matter

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to diagnose chronic malarial cachexia.   It is chiefly to be
confounded with grave primary or secondary anæmia, or
with leukæmia, tuberculosis, and psuedo-leukæmia.   The
malarial process may usually be distinguished from splenic
anæmia by the presence of pigment and parasites in the
blood.   In some instances, where these are not to be found,
the enlarged spleen, the grave anæmia, the hæmorrhagic
tendency, and the dropsical effusions present in both condi-
tions may render the diagnosis almost impossible without
appealing to the history of the patient.   The progress of such
cases is usually decisive.   The malarial cachexia responds
generally, slowly but progressively, to treatment.   Thus
one may see a spleen which reaches beyond the umbilicus,
and almost to the pubes, diminish under treatment until it
is only just palpable, while the blood returns to the normal
condition as regards the number of its corpuscular elements.
Examination of the blood will also allow of a diagnosis from
leukæmia.   It is impossible to effect an absolute differential
diagnosis between post-malarial anæmia and some other
secondary anæmias.   The tendency in the post-malarial
anæmia to a diminution in the number of leucocytes is
always marked, while a relative increase in the large mono-
nuclear elements is very suggestive.   Post-malarial nephritis
has no special characteristic to distinguish it.   Comatose per-
nicious fever when seen at the state of unconsciousness is
mistaken for septicæmic form of plague ; though the signs
are at first sight identical, but the history of previous illness,
jaundice tint of conjunctiva and examination of blood, etc.,
render the diagnosis easy.

   Mixed infections and other complications.—A certain
diagnosis can only be made in some of the mixed infections
already referred to by the discovery of the parasites, and
the persistence of the complicating process after the dis-
appearance of the organism under the administration of
quinine.   Thus, a persistence of the characteristic symptoms

after the clearing up of the complicating malarial process would allow of a diagnosis of typhoid fever. The usually well-known symptoms will serve to distinguish acute rheumatism, tonsilitis, paratitis and the exanthemata from malarial fever. The diagnosis depends in the case of pneumonia more upon the physical examination, as it is well known that the malarial parasite is incapable of producing actual consolidation of the lungs. Pleurisy is also recognised by its classical physical signs and subjective symptoms. The malarial poison may or may not be directly responsible for the occurrence of diarrhœa or dysentery during the active malarial process. The presence of the *ameoba coli* in the stools is evidence of a complicating process; while in other cases a positive diagnosis cannot be made until a response to quinine is observed in connection with diarrhœa in acute malaria.

Prognosis.

So far as the probable outcome of the illness is concerned, the prognosis in tertian and quartan fevers is almost invariably favourable. It is only very exceptionally that one sees a case in which actual pernicious symptoms are present in tertian and quartan ague. Without systematic and careful treatment relapses and grave cachexia may follow a cachexia which may well lay the patient open to the gravest secondary complicating diseases. It is not improbable that repeated malarial infection in these cases may be followed by a fatal chronic nephritis. The prognosis is perfectly good in ordinary cases of æstivo-autumnal fevers which come early under treatment. The latter must be more active and longer carried out than in the regularly intermittent fevers. Cachexia and grave post-malarial anæmia are more likely to follow upon imperfectly treated cases. The prognosis is extremely grave and unless active treatment be instituted, it is usually wholly unfavourable

in all cases in which pernicious symptoms have developed. On the other hand, the prognosis is usually favourable if active treatment has been begun during a pernicious paroxysm and no succeeding paroxysm has occurred within 48 hours. In a patient first coming under observation in a pernicious paroxysm an entirely favourable prognosis can never be given for at least 48 hours after the beginning of treatment. It is always possible that a single pernicious paroxysm may be succeeded, despite treatment, by another upon the following day. The prognosis is always extremely grave in malarial *hæmoglobinuria;* indeed, the dangers of a fatal outcome are not past until the disappearance of the urinary symptoms and of the fever. If the patient can be persuaded to remove to a more healthy locality, in the more severe grades, recovery is extremely slow, and at time almost impossible ; in the mild grades of chronic malarial cachexia the prognosis is good as the patient can be made to adopt a properly hygienic life. Of an extremely grave character are often the anæmias following malarial fevers. The prognosis is always as bad as it could possibly be in those cases where the blood shows the characteristics of true pernicious anæmia, and in those instances in which the nucleated red corpuscles are scanty or absent and the leucocytes are diminished in number. An unusually unfavourable course is apparently pursued by secondary infections occurring in individuals suffering from malarial cachexia ; and the possible unfavourable effect of the co-existing malarial infections alone influences the prognosis in the various complications of malarial fever.

CHAPTER XVII.

EPIDEMIOLOGY AND PROPHYLAXIS.

EPIDEMIOLOGY.

There is no part of India where there is no malaria permanently. There is no town in India which is free from it. The only question is the degree of amount which depends on the condition of the situation. The study of the last Epidemic of India, which had drawn so much attention, began from the middle of September 1908, and lasted till December 1909, would serve our purpose in tracing out the predisposing causes of epidemic. It was somewhat connected with the climatic influence, in the year 1907, there was no rain, and the soil was very dry and practically obliterated mosquito breeding places, and there was no epidemic of Malaria. The partial rain of 1908 favoured the excessive breeding of mosquito, just as a piece of land when left uncultivated for a year and the harvest of which after that year is more abundant than usual. The analogy applies to mosquito-breeding. As the soil and water play only secondary and indirect part, so it is favourable to the life and development of the malarigenous mosquitoes. It may be, in fact is, the habitant of the eggs and larvæ of the mosquito, which eventually become malarigenous. Therefore, soil and water pass into the direct causes of epidemic, that is to say, those which we term *predisposing*. Again, it is known to us that man and mosquito are the sources of malarial infection which circulate from man to mosquito and *vice versâ* ; therefore malaria is a typical contagious disease, and according to Celli, the air is the carrier of malaria, inasmuch as it is the vehicle of the malarial mosquitoes.

PREDISPOSING CAUSES.

No epidemic can be thoroughly understood unless the causes which are favourable to the development of an epidemic

are recognised to the full. These very complex causes I divide into (I) Individual, (II) Local, and (III) Social causes of predisposition.

I.—THE INDIVIDUAL PREDISPOSITION.

It may be stated that no race, either black or white, rich or poor, old or young, is immune from malarial infection. It all depends on the habits of life, physical strength, and the state of health of the individual. There are, however, places where malaria is very severe all the year round, and certain individuals escape malaria who are always exposed to the infection. This may be explained thus: - That the strength of the individual resists infection or may be somewhat connected with immunity. It is generally observed that chilling of the body, along with the disorder of the normal functions of the liver predisposes both to the onset of the primary infection, and to the relapses. The mortality has lately been much higher than usually for the simple reason that the poor people, especially the tenants and some better class of people who have had no adequate treatment, as the poor people can't afford, and the better class have an aversion to English medicines.

II.—THE LOCAL PREDISPOSITION.

(1) Condition of place includes the following : —

(a) Soil.—There is no quality of soil which can be said to be incapable of favouring the development of malaria, inasmuch as in this sense the soil does not act *per se*, but only so far as it may become a reservoir of water. Besides it can no longer be admitted that a simple stirring up of the soil in malarious places liberates the malarial poison. The soil of a certain locality is moist owing to the peculiar situation, and any alteration with the addition of rain favours the hatching of the mosquitoes.

Palpably, any kind of soil may become mala-
rious when water, air and certain vegetations
are present for the propagation of larvæ of
the mosquito.

(*b*) **Water.**—That is necessary for the development
of malaria, inasmuch as it is necessary to the
life of the larvæ in stagnant and slowly-run-
ning water which exists in the villages. The
water of the houses which has undergone
putrefaction and that the ground water on the
surface of the soil, even though its area is
small, are favourable for harbouring mos-
quitoes.

(*c*) **Agriculture and malaria.**—Marshy vegetation,
composed of *canes, weeds, fungi, algæ, water-
lilies, Nurkuls* (bulrushes), and many others, is
very favourable to the life of larvæ. It is
observed in the jungle that a great many shady
trees and plants are favourable resorts for adult
mosquitoes. Sleeping under these trees one
catches fever very readily. There are many
plants, for which mosquitoes have affinity, and
there are many for which they have detestation.
It is said that Castor-oil plant which is largely
cultivated here, is hostile to mosquito. On
particular observation it was not seen anything
peculiar. Irrigation may favour the develop-
ment of malaria by offering room for the
existence of the larvæ of anopheles. Thus
irrigated lands in malarious places, whenever
the water becomes stagnant, and choked with
certain amount of vegetation, constitute the
hot-bed of the larvæ. The rice-field is known
for being an abode of mosquitoes, though I failed
to discover the larvæ within a field, but there

are swarms of adult mosquitoes. In confirmation of this, cases of malaria amongst the workers of rice-field have been seen very common. It is also said that cultivation may partly correct the local predisposition to malaria, but it does not destroy it, because the larvæ of the Anopheles are found in the ditches round about the cultivated area.

(2) **Influence of the season.**—The change of season has long been recognised as having an influence on the production of malaria. A connection has been asserted to exist between rain and malaria, which has already been referred, that is to say, a heavy rainfall in the month of July, August and September removes malaria, as all the breeding-places are washed away from the vicinity. This phenomenon was particularly noticed in a country place which was notoriously malarious owing to its own situation, so much so, that I had not seen a single soul there who had no attack of fever, and all the inhabitants there were sickly, pale-looking, and most of them had large spleen. The place is situated within two rivers, and during the rainy season that country is always flooded, and some months after the flood, the first attack of malaria ceases for some time. On the other hand, a partial rain with a break in the interval favours the epidemic of malaria, being suitable season for propagation of larvæ. Want of rain or dry season removes malaria altogether as during hot months one scarcely sees a malaria case ; if there be heavy showers of rain in the winter, there is malaria in the month of April, May and June. The statistics of the malarial cases which have been asserted in the previous pages, appear to show that malaria is endemic during the whole year. The question of maximum and minimum comes in the way which depends according to the season of the year. With some oscillations, however, it remains low from December to April of the following year. In the month

of May, June, July and August it declines. In the month of September, October and November the true epidemic of malaria bursts forth. This is the real malarial season, that is the season of primary infection. As to its sequels, recurrent fever due to a want of proper treatment, exists all the year round.

The temperature has also some relation to malaria, as it is shown by the evidence that a sudden appearance of fever in the month of September prolongs to the beginning of winter. In the same way the difference of temperature between day and night, so characteristic of malarious places, must produce that predisposing cause termed above chilling of the body ; and the winter cold also concurs in regulating the quantity of the mosquitoes, and therefore also of malaria.

III.—THE SOCIAL PREDISPOSITION.

The *social* and *economic* conditions of India have a close connection with an outbreak of epidemic. I therefore analyse briefly the social and economic causes of predisposition to Malaria —*food, housing, clothing, work* and *education*.

(1) **Food.**—The food of our poor peasants for almost the whole year consists chiefly of maize and other cereals with a deficiency of nitrogenous and an excess of triple substances. The effect in nitrogenous constituents manifests itself in the inevitable and enduring physical deterioration, which causes the starved appearance of our rural labourers, though they eat wheaten bread during the period of excessive work and not always. Even this insufficient food was not obtained by them during the famine; therefore fever during famine is a very old story on the lips of the old Indians. The food of our better class of people is also not so wholesome as to scientifically maintain the general health in a state of robustness, and consequently the general vigour of the body is undermined and, being careless in their habits, are unable to resist any infection. Therefore people are predisposed to malarial infection.

In former days, people used to have a good supply of whole-some food, and no worries, and they were strong and healthy enough to withstand the evils of unavoidable circum-stances of the surroundings. It is strikingly evident that the Europeans in India who take sufficient amount of precautions, whose food and surroundings are also whole-some, have not been victims to the epidemic of this country.

(2) **Housing.**—Malaria is a domestic epidemic. The enormous importance of this social factor is therefore evident. The most common type of habitation of the poor peasants and menials in our malarious districts, is the hut. There is nothing fine about such huts, which are surrounded by any amount of filth, except the smoke given off by the fire of cooking which drives away the mosquitoes. Almost all these people sleep in the open air, except those sleeping under the shade of trees. The houses of the better class are generally constructed of bricks, etc., but kept up without regard to prophylactic rules against malaria.

The houses of the *Hindu* community are exceedingly damp for want of sunlight and ventilation, and conditions inside of the houses are all favourable to serve as the haunt of mosquitoes. The houses of the *Mahomedan* community, though spacious and ventilated, are untidy and the ordinary rules of hygiene are neglected.

(3) **Clothing.**—The clothing worn by the poor for the most part is very insufficient either to prevent the chills, or to protect them from the bites of the mosquitoes. The children specially are, during the whole year, naked, and it is they who pay the heaviest tribute to malaria.

(4) **Work.**—In the months of October and November the enormous amount of agricultural work is done, such as ploughing and sowing seeds, etc., in the places where there are homes of anopheles, and other workers sleep in the open air, and there is a great difference in the tempera-

ture of day and night, thus at that time workers are exposed to the bites of the mosquitoes thus giving rise to the epidemic.

(5) **Education.**—Through poverty and want of knowledge as to the source and vehicles of infection, and also through ignorance of the means of protection, the epidemics arise and flourish. The prejudice against the specific remedy, quinine, is unsurmountable, due to the ignorance and conservation of the people. They won't take quinine in spite of the warnings until they fall ill.

PROPHYLAXIS.

The greatest benefit is to be derived in malarial fever from prophylactic measures ; and these belong in part to the domain of public hygiene, and in part fall within the scope of individual effort. Those dealing with proper drainage, cultivation of the soil, and so forth, would require an article of even greater length than this for their full consideration, so they cannot be described here. The individual must adopt certain measures, which may protect him in the most malarious districts. I summarize the prophylactic means to be directed against the (I) *predisposing* and (II) *infective* causes.

I.—Predisposing Causes.

(1) *Measures against individual predisposing causes.*

If it be necessary to visit, temporarily, notoriously malarial districts, let a person so far as possible, choose the season of the year at which the fevers are least prevalent. The dwelling should be sought upon ground as high and as dry as possible. Exposure at night in damp or marshy districts should be avoided. Despite the experimental evidence that infection may occur through the gastro-intestinal tract, it is prudent to boil all drinking water coming from malarious districts.

Medicinally, quinine in small doses will prove protective against infection.   Monti has reported good results from the administration of the sulphate of quinine in doses from five to six grains every other day ; but Sezory (Modern Medicine, 1892) says that under most circumstances even a little over two grains will be sufficient for the purpose.   If the district be extremely malarious the various simple wines containing cinchona are insufficient protection, and it is advisable to take several grains of quinine daily.   The destruction of the mos-quitoes should be effected as far as possible; and the indivi-dual should protect himself from their bites in the usual way

Habits of life should be corrected by not sleeping in the open air, not keeping light in the room with the windows open, and by having mosquito nets and punkha in the room, and by using perfumes on one's person, such as Eau de Cologne, etc., and one should bathe every morning with soap and water, and wear proper clothing to protect from chill.   If possible, the night should be passed on the upper storey of the house, and the functions of the liver be regulated.

(2) *Measures against local predisposing causes.*

If nothing can be done against the local predisposing conditions of the season, much can be done against the local predisposing conditions of the places ; of course, a great deal depends upon money, enlightenment, and knowledge of the people, among whom it is necessary to remove the principal predisposing causes, such as stagnant water and impure air. The essential condition in any scheme for the sanitary improvement of a malarious place is that it should prevent the lodging of larvæ and eggs of mosquitoes.   If possible the following measures may be tried.

Treat all anopheles' resorts frequently with kerosine or tarry solution during the whole of the dry season and useless excavations and pits should be filled in, and wherever there are permanent bodies of water, small fishes such as

minnows, sunfish, killfish, and *top minnows,* which are ene-
mies of the larvæ, should be cultivated, therein. In many
cases simple introduction of tide into low-lying regions
will bring about sufficient movement of the shallow stagnant
water of the marshes. These measures should be tried in
the urban places along with urban sanitation, such as washing
off the surface water, sewage and pavement of the streets.
The villagers should not have cattle-sheds within the com-
pounds, and the walls of the huts which are generally of
mud should be uncovered in the hot season to have them
dried in the hot sun In the malarial towns, streets should
be paved and surface drains should be washed and swept,
and roads should be sprinkled with petroleum ; cisterns, rain
barrels, and other receptacles which are found within the com-
pound of a house in which mosquitoes are apt to breed
should be kept covered.

Housing.—The builders of new houses must select
building sites in elevated places, and construct double-storeyed
ones. The walls and floors should be cemented and the com-
pound within the boundaries of a house should be paved and
have underground drains and sink for refuse. The com-
pounds of larger houses have less vegetation, and there is
no harm in having large trees ; if there be garden it must be
looked after.

I may mention here some prophylactic means which
may be utilized :—

(1) Kerosine.—It may be used in the drains. Its
value as a prophylactic of mosquitoes is very valuable.

(2) Petroleum —The roads should be layed with it.

(3) Sea salt—Is also hostile to the mosquito larvæ.

(4) Benzoin or Loban.—This substance is very
commonly sold in the Bazaar, and people very commonly
use it. This is very frequently burnt by people in closed
rooms, as its fumes destroy all the mosquitoes in the
room.

(5) **The flower of Gutta-percha tree.**—The peculiarity of this flower is that when ignited in a house at one place, the fumes and the smell of its burning make all the mosquitoes fall dead on the ground from all parts of the house.

(6) **For maldehyde.**—This chemical destroys mosquitoes; it may be utilised by washing the doors, windows and places where mosquitoes abide ; the solution is made in sufficient strength five per cent is, as a rule, quite enough for the object.

(7) **Flower of genda** (*Tagetes patula, Linn*).—This flower is commonly grown in India. It is said that mosquitoes have a great dislike for its smell. When kept within a room no mosquitoes are found therein.

II.—Infective Causes.

An attempt should be made towards destroying malarial germs which are the causes of infection.

When the theory of " Man to mosquito and mosquito to man " is correct, the first prophylactic measure is " Isolation " and should be taken directly when the diagnosis is confirmed. In a malarious place a person affected by the fever is very dangerous to others and should therefore be isolated. Malaria is a true contagious disease, because the patient is the source of infection to the mosquitoes, and subsequently human beings. Malarial patients can be isolated in any place where there are no mosquitoes, and experience verifies that old chronic cases with malarial cachexia whenever removed to other places, get over the disease.

There is no drug in the *Pharmacopæia* which has such valuable and precious property as quinine has, being curative and prophylactic for the disease, it is singled out. It is the surest and easiest prophylactic for malarial epidemic. It is much more suited for the people of this country than anything else. I have obtained such excellent results, not in one case, but in thousands of cases of quinine used as preventive to malaria. But at the same time I don't follow the general rule that one single dose of 10 grains or 7 grains once a

week is enough to keep that person immune for that week. I am hopelessly disappointed with this regime. It is not enough for Indian constitution and surroundings. As far as my experience is concerned with this is, that unless 5 grains for adult and 2 grains for children, in the form of sulphate of quinine is taken early every morning on empty stomach, its efficacy will be far from expectation. I have come to this conclusion after making an observation in several other ways. I am obtaining excellent results in notoriously malarious places. I remember a schoolboy who was suffering from remittent fever, consulting me during an epidimic year who lived in the hostel of the school, where a single dose of quinine was given to each boarder, once a week. He had his quinine on Monday, and he was attacked with fever on the afternoon of Friday. There are numerous instances like this.

The effect of quinine on malarial parasites at all stages of the disease is a well-established truth. The study of physiological actions of this drug on the circulation and blood reveals the fact that quinine diminishes the power of oxidation of red corpuscles and also disinfects the blood. These effects lasting to a certain limit of time have relation with its prophylactic action to malaria. Why does quinine act as a prophylactic to malaria ?

I may suggest that a dose of quinine on alternate days might serve the purpose. There is no harm in using quinine every day, as it acts as a very good tonic. I have noticed people who take quinine every day possess better appetite to enjoy their food, as it stimulates the gastric secretion, and persons begin to have colour on the face. There as good many people who I know have got a prejudice against quinine and they would not consent to take it under any circumstance, but the poor have no objection to it ; for them tact and persuasion are necessary.

It must be kept in mind that cases of *idiosyncrasy* of quinine do occur, that is, a small dose of it produces

symptoms of quininism, for such cases I have found excellent adjuvant in coffine citras or a cup of coffee.

Finally, a word must be said on education that a doctor or administrator could do nothing unless there was a willing co-operation on the part of the people. The people should be taught to appreciate the saying of science, and it could be accomplished during school training and through the newspapers and society. The diffusion of knowledge regarding the epidemiology and prophylaxis of the infectious disease ought to be undertaken by the social reformers to contradict old prejudice.

Administrative Measures

Any administrative measure, undertaken in the line of prophylaxis which must have regard to its success and failures, should be such as to encounter the physical and the economic conditions of the country. The majority of the population of India is poor, and they mostly pay a tribute to malaria, and so their lives should be protected and saved, and for this, unless a *gratuitous measure* is established during the epidemic period, success will be far from it. For free supply of quinine there must be appointed a staff of quinine suppliers. At every urban town a hospital assistant and a number of compounders with leaflets of instructions should be stationed. The compounder should pay house-to-house visits (and persons to persons), supplying quinine to them every morning ; and persuasion and tact are of vital importance in making them swallow it. The best method of taking quinine is in the form of pills, that is, mix up 5 grains of sulphate of quinine with a little citric acid and no one will object to this.

The tabloids are no good. They pass sometimes undissolved with fæces. Another palatable method is to mix quinine with fresh lime-juice and sugar. I am also in the habit, just to gain the confidence of the people as they approve

it, in advising to take a good deal of chilly and acid with meals. The acid acts on the liver and chilly stimulates the circulation which may prevent the chill.

The hospital assistant should supervise the duties of compounders, and treat malarial cases wherever they occur. This is meant for urban districts, and for the towns I would say " Education."

CHAPTER XVIII.

TREATMENT.

MANAGEMENT OF THE DISEASE.

General measures.—In the treatment of malarial fever there are certain general hygienic measures advisable, and sometimes very important. In all cases it is prudent to keep the patient in bed, if possible, for twenty-four or forty-eight hours : in the more severe æstivo-autumnal fevers it is absolutely necessary. The simple regularly intermittent fevers often show a temporary and sometimes permanent spontaneous recovery following rest in bed, without further treatment. In hospital practice the patient should be kept in bed until the entire disappearance of the fever, whether it be intermittent or subcontinuous. The fact that the patients are so much more readily kept at rest may possibly account for the more satisfactory results of hospital treatment in malarial cases, in part at least. In the case of the patient being resident in a very malarious district, it is always important, if possible, that he should be removed to more salubrious surroundings. Thus, recovery from chronic cachexia is greatly favoured by removal into higher and more healthy localities. In some instances of advanced cachexia the removal may be absolutely necessary. In the ordinary acute malarial fevers it is generally perfectly possible to treat the case in the malarial district itself. The patient should be kept, while under treatment, in one of the upper stories of the house ; he should be prevented from subsequent exposure to infection, if possible, and be warned against remaining out of doors at night during convalescence. The patient may be allowed an ordinary nourishing general diet in the simple intermittent fevers. During the paroxysms, which last but ten or twelve hours in all, the patient need

not be forced to eat ; it is generally well that liquids, milk, broths, and soups should be taken in small quantities. Stimulants may be administered symptomatically. In the more severe subcontinuous fevers, where there is usually complete anorexia, the patient may be given liquids of all sorts, soups, milk, and broths, at short intervals ; while, if he be hungry and there be no gastro-intestinal disturbances, there is no contradistinction to soft solids and eggs In cases where there are marked gastro-intestinal symptoms great care must, of course, be exercised with the diet ; it should be entirely restricted to broths, boiled milk, albumin water, and so forth. Exposure to the night air is held by the inhabitants of some malarious districts, and probably justly too, to be injudicious : this observation is based upon experience. It may be unwise for the patient in such regions to be allowed to sleep with his windows open. If the patient be in a healthy district and be accustomed to living and sleeping with open windows, there is no reason why a change should be made during the existence of the fever. Provided the sufferer be accustomed to such air beforehand, there is no fever which we know of at present which is unfavourably influenced by fresh air and suitable ventilation of the sick-room.

Quinine.—This drug still occupies the front rank amongst all medicaments that have been advanced for the treatment of malarial fever : indeed, it is a real specific for that affection. Quinine, in the form of cinchona bark, was introduced into Europe, in 1640, by the Countess Del Cinchon, wife of Del Cinchon, the Spanish Governor of Peru, who had recovered from a severe attack of intermittent fever after taking a powder administered by a corregidor of Loxa. So far as is known, this substance was first used by the Indians in America as a remedy against malarial fever. The powder, which was known at first as the " powder of the Countess," and afterwards as the " Jesuits' powder," for the reason that

it was introduced into general use by the Jesuits in Rome in 1649, was prepared from the bark of a *Peruvian* tree. This was for years known as *Peruvian* bark, though its official name, Cinchona, is derived from that of its introducer to the Eastern hemisphere It was first administered in the form of the pulverised bark, the cinchona powder, which contains, in addition to various *alkaloidal* substances, a considerable quantity of tannin. The various salts of its active principle, quinine, are now in use, and the pulverised bark abandoned. The exact mode of action of quinine remained unknown for centuries after its introduction and after its specific effect in malarial fever has been discovered. As far back as 1867, Binz (Centralbl. f. de. Med. Wiss. 1867, p. 308) correctly concluded that the efficacy of quinine in paludism depended upon its action as a protoplasmic poison upon some lower organism which he assumed to be of the nature of the cause of the process. The extremely toxic action of quinine upon the infusoria was at that time clearly demonstrated. Since the development of our knowledge concerning the malarial parasite, it has been possible to study, to a certain extent, the direct action of quinine upon the hæmatozao. Laveran noticed the immediate disappearance of the parasites following the administration of quinine, and in 1881 asserted that it is because it destroys the parasite that quinine causes the disappearance of the manifestations of paludism. He showed that by allowing a solution (1: 10,000) of quinine to run under the cover-glass the movements of the parasite were immediately arrested, as they are when any other protoplasmic poison is employed. The behaviour of the tertian and quartan parasites to quinine has been carefully investigated by Golgi. He observed that after the administration of quinine the quartan organism, in its endoglobular stage, shows a coarser granulation with a metallic reflex, while the protoplasm shows a definite cloudiness. At times one may see abortive segment-

ing forms which are smaller than the normal, with a lack of regularity and fewer segments. The pigment also may not collect as sharply in a clump in the middle of the parasite. In the tertian parasite the changes are more marked, owing to a greater normal activity of the organism The body is round and immovable, and shows a sharper outline than usual. While the pigment has a peculiar metallic reflex and tends to collect in clumps. Full-grown tertian forms may present a large transparent swollen condition with very active movements of the pigment granules. Sometimes the pigment may collect towards the periphery, leaving a hyaline space in the middle Mannaberg asserts that three hours after the administration of 0·5 of quinine the amœboid forms of the tertian parasite show a marked diminution of their activity. In several hours more the number has greatly diminished, while many of these present are fragmented, resulting in the presence of several separate spherules in the red corpuscles. Full-grown forms show a cessation of the movements of the pigment, the body having a somewhat refractive homogeneous appearance. Large hydropic forms with active pigments may also be seen. These two latter forms may occur normally during the paroxysm, as Golgi and Mannaberg also assert ; they are probably degenerative forms. In the case of the tertian parasites the somewhat greater refractiveness of the organism, the collection of the pigments into clumps, and the cessation of active movements as well as the presence of a greater number of fragmenting forms, have been seen. Some very interesting studies with stained specimens have been made by Romanowsky (Cent., Bakt., 1892, XI, Nos. 6 and 7, 219 ; and St. Pet Med. Woch., 1891, Nos. 34 and 35) and Mannaberg. Both observers noted the loss of affinity for colouring matters in the chromatin substance of the nucleus. They also observed that in the segmenting forms, after quinine had been given, the greater number of the segments show no nucleoli ; and

these changes in the nucleus they believe to be evidence of a necrotic process. The segments without nucleus Manna-berg termed "still-born," Marchiafava and Bignami, studying the æstivo-autumnal fever, note that the administration of quinine is followed by an increase in number of shrunken, brassy-coloured corpuscles. They believed that further development of the included parasite was impossible. Bacelli (Deut. Med. Woch., 1892, No. 32, 721) noted that in æstivo-autumnal fever, after the intravenous injection of quinine, there was an increase in the activity of the small amœboid forms, which often disappeared within twenty-four hours without showing any outward sign of degeneration. The vast majority of those who have been able to test the action of quinine upon the malarial parasite will agree with Golgi that in tertian and quartan fever quinine acts most markedly on the free young segments, less upon the more advanced forms where the red corpuscles are in greater part destroyed, and the least upon the young endoglobular forms. If quinine be given several hours before the paroxysm, it will not prevent segmentation, but it will destroy the new group of parasites, the fresh segments. Segmentation takes place, toxic substances are produced and enter into the blood-stream, and the chill follows, being at most a little modified or retarded. The further development of the new group of organism is prevented, and on the following day no parasite whatever may be observed. The same appears to obtain in the case of the æstivo-autumnal parasite, the maximum and most rapid action of the remedy being exercised on that phase of the endogobular life of the parasite which follows the completed segmentation. Golgi says that, in the case of tertian and quartan organism, the segmentation cannot be prevented if quinine be given when the parasite has reached the preparatory stages. The drug acts on the amœba of malaria during those phases of its life in which it develops and absorbs nourishment; when the nutritive activity comes

to an end, the transformation of hæmoglobin into black pig-ment having been accomplished, and the phase of reproduc-tion begins, then quinine becomes inefficacious against this process. Quinine should be in *solution* in the blood at the time of the setting free of the fresh parasite, *i.e.*, during and several hours before the paroxysm in order to combat best the further development of a group of malarial germ. In ordinary tertian or quartan fevers, with moderate regular daily dose of quinine, the parasites will usually wholly disappear from the peripheral circulation within three days. In æstivo-autumnal fevers the time may be a little longer. The crescentic bodies remain in the blood long after the disappearance of all other forms of the parasite, being affected slowly, if at all, with quinine.

Regarding the effects of the remedy upon the patients, in small doses, such as are ordinarily required therapeutically, quinine causes no subjective symptoms. In somewhat larger doses, however, it produces at times a ringing in the ears, roaring or sometimes tinkling noises, and, finally, more or less deafness. Larger doses are followed by a dimming of the vision, even to complete blindness. Ringer has noticed that this may sometimes begin in one eye, and, indeed, exist for considerable time on one side only. The pupil is usually dilated In larger doses a severe frontal headache, with giddiness and staggering gait, delirium, and great muscular weakness, may follow, and, finally, in still larger doses, convulsions and death. Sometimes larger doses of quinine are followed by certain cutaneous disturbances, urticaria at times occurs ; and Ringer describes an intense general ery-thema similar to a scarlet fever eruption and followed also by desquamation of the skin.

There is a proper method of administering quinine. Like another commonly used and extremely valuable drug, digitalis, quinine, which is our mainstay in malarial fever, is very frequently abused. Laveran well says. " In a general

way it may be said that in malarial districts far too much sulphate of quinine is given to patients who have no need of it, while a sufficient quantity is not given to patients suffering from paludism." The very degree of its efficacy, as in the case of mercury and Iodide of potassium in syphilis, is probably accountable for the lax manner in which it is frequently given. When one or two doses are followed by a complete disappearance of the symptoms, the immediate relief is so great, that the patient fails to recognise the importance of continued treatment, and lays himself open to repeated relapses by abandoning the regular régimé. The determination of how and in what form quinine should be exhibited in any individual case is of considerable importance. The ordinary way of administration is by the mouth, and the common form in which it is given is as the sulphate. The sulphate of quinine is very slightly soluble in water, but quite readily soluble in dilute acids. The best manner to administer this form of quinine is in water containing a sufficient quantity of dilute *hydrochloric* or *nitromuratic* or *hydrobromic* or *sulphuric acids* (dilute) to hold the salt in solution, it being customary to add one drop of the dilute acid to one grain of the salt. The extremely bitter taste is sometimes an objection in sensitive patients: this, in the case of the quinine powder, may be partly obviated by mixing with an equal quantity of powdered ginger, or by taking a mouthful water previously and then by putting the powder in the mouth to be swallowed at once. The drug may also be administered in the form of pills or in capsules. Quinine pills are convenient, but are open to the common objection that in many instances the commercial pill is a highly insoluble object. Thus it is not at all infrequent in dispensary practice for the physician to be consulted by patients with simple intermittent fever who have taken quinine pills without effect, while the *solution* or the powder has an *immediate* result. For more rapid action the quinine may be administered hypo-

dermically. The solution adapted for hypodermic injections is the following : Quinine sulphate, grain 15 ; Acid sulphur. dil. q-s and Distilled water q-s, ad ℥iiss 5—30 minims for a dose. We can also use more dilute solution, in order to render the injection less injurious. The solution should be clear and the instrument and the skin of the part where the injection is to be given should be rendered aseptic. The injection may be made in the back or abdomen or gluteal region, in which situation some prefer to give it intramuscularly as being less painful or entirely painless. Strict asepsis will prevent the occurrence of tetanus, which in former times not infrequently made its appearance, following inflammation at the point of puncture, usually a few days after the injection. Although more or less troublesome subcutaneous indurations are sometimes unavoidable, severe eschars, abscesses, and even worse local injuries can be avoided by observing the precautions mentioned above. When prompt and energetic treatment is necessary, Bacelli suggests a method of intravenous injection of quinine. For this purpose most soluble salts other than the sulphate must be used. The formula which he recommends is the following : Hydrochlorate of quinine, gr. xv ; Chloride of sodium, about grain 12 ; Distilled water, q-s ad ℥iiss. The solution must be perfectly clear, and should be tepid. Before giving the injection, a large bandage is bound above the elbow, as in the case of venesection, in order to swell the veins of the forearm ; into one of these veins the needle is introduced, and then, the bandage having been removed, the fluid is slowly pushed in. A swelling at the point of injection is a sign that the needle has not been properly introduced into the vein. Bacelli says he has cured all his cases of pernicious fever in this way after 24 hours, there being no return of the pyrexia, nor relapses. Others do not speak so well of the methods. After the needle has been withdrawn, the stab wound should be carefully closed with *collodion.*

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Another convenient way in which to administer the remedy is in the form of the *bimuriate of quinine* and urea, which contain nearly 80 per cent. of quinine and is soluble in less than its own bulk of water. It may also be given by the rectum ; but quinine is seldom used in this way, except in the case of children and as a last resort. One may readily perceive the time at which, theoretically at least, the drug should be given, if we take into consideration the studies of Laveran, Golgi, Mannaberg, and others concerning the effect of quinine upon the parasite, and then remember the close relation between the development of the parasite and the symptoms of malarial infection. Inasmuch as it has been shown that quinine acts most effectually upon the young extra-corpuscular parasites, it would seem fair to conclude that the period just before or during the paroxysms should be that at which quinine might be administered with most effect, and, as has been clearly shown, this is actually the case. A dose of quinine shortly before a paroxysm in the regularly intermittent fevers will not affect that paroxysm, but will prevent a recurrence of the succeeding one dependent upon that group of organism   Thus, a single moderate dose of quinine, given just before or during a paroxysm in single tertian or quartan infection, will cause a general disappearance of the symptoms, while in the case of a double tertian injection it may often be seen to change the type of the fever from quotidian to tertian. Therefore, in such an instance, the paroxysm expected upon the following day will occur, but that expected in 48 hours will not appear, the greater part of the group of parasites having been destroyed   Though the parasites are much more resistant to the action of quinine than those of the regularly intermittent fevers, the same has been shown to be true in æstivo-autumnal fevers. In the case of the regularly intermittent fevers it is generally advisable to place the patient upon regular treatment with quinine. If it be possible to

keep the patient in bed, small doses will often be sufficient. Thus, 3—4 grains three times a day will, in many instances, be followed by a disappearance of the symptoms In practice we may give, according to the severity of the case, from 4 to 6 grains three times a day. If in tertian fever the patient be seen on the day before the paroxysm, 5 grains generally, three times a day, will, if the patient be confined to bed, prevent even any succeeding paroxysm. One may predict, almost with certainty, the entire disappearance of the fever after this. If the patient be seen first just before an expected paroxysm or during the attack, it may be well to give a single dose (grain 10), and follow this by smaller doses (grain 5) three times a day. If the paroxysms have been severe, it is sometimes wise to give large doses of the drug (grain 10—15) during the first days of treatment at the hour when without treatment the paroxysms might have been expected. Treatment with small doses in 24 hours should be continued for at least three weeks, although the parasites in tertian and quartan affections disappear from the blood generally within three days. This question will be fully dilated later on in a separate chapter. As a rule, large quantities of quinine must be given for the treatment of æstivo-autumnal fever. In ordinary cases where no pernicious symptoms have developed, one may start treatment with 5 grains every four hours In most cases under such treatment, fever will entirely disappear within three days. If symptoms of cinchonism develop, the dose may be reduced. If the patient come under observation during a paroxysm, or if the history be obtained of a severe paroxysm having recently occurred, it may be well to begin with a larger single dose. Thus, during or just before, a paroxysm 10 grains may be administered, followed by 5 grains every four hours. If severe nervous manifestations accompany the paroxysm and the development of pernicious symptoms be feared, it may be well to administer the quinine

hypodermically or intravenously. It is rarely necessary to give larger doses than 15 grains. It may rarely be necessary to give several doses of this size at intervals of several hours during a long-continued paroxysm ; usually two or three doses at intervals of four hours are sufficient, while afterwards it will be possible to give smaller quantities (grain 5) every four hours. Such doses will usually prevent the recurrence of a paroxysm due to this group of parasites. It is possible that a second large group of parasites, which all treatment has failed to influence, may, on the following day, produce a fatal paroxysm. The same course should be pursued during the succeeding paroxysm It has long been a well-recognised fact that if the patient survive the second paroxysm after the beginning of treatment, ultimate recovery is usually assured. In true pernicious paroxysms the experience of Bacelli would seem to show that the intravenous injection of quinine is by far the most efficacious. In the case of malarial hæmoglobinuria, the same general rules which apply to the treatment of other pernicious fevers hold good ; but it will be dealt with separately later on. It should be noted that certain observers believe that large doses of quinine exert a distinctly injurious influence upon the blood, aggravating often the destruction of the red corpuscles. The view of Plehn is not generally accepted by the majority of clinicians ; in special articles he goes so far as to advise an expectant treatment in these cases, asserting that recovery is more likely to result under careful nursing and general treatment than under the administration of quinine.

There are various other cinchona derivatives that have been advanced as substitutes for quinine in the treatment of malarial fever ; but their efficacy, however, is so far below that of the various salts of quinine, that it is scarcely advisable to exhibit them. Thus *cinchonin*, *cinchonidine*, and quinidine have been recommended. Finally, we must note that

there are certain contra-indications to the use of quinine; the susceptibility to the drug varies greatly in different individuals. Relatively small doses produce cinchonism in some persons, while others are extremely tolerant of the drug. In the majority of instances in which complaint is made, it is based upon the fact that the drug has been administered in injudiciously large doses. Indeed, it is very seldom that one comes across a case in which it is impossible to administer quinine in sufficient doses to combat ordinary malarial manifestations without serious symptoms. Cases of this nature are extremely rare, and there are instances amongst Indians in which individual susceptibility is contra-indication to the administration of quinine in malarial fever. It is advisable to exhibit the drug in a form unfamiliar to the patient, for the prejudice against this drug is very strong in the mind of some individuals.

Methylene blue. — By some methylene blue is said to be the most valuable remedy next to quinine in malarial fever. It was first employed, in 1891, by Guttermann and Ehrlich (Berl klin Woch., 1891) who were led to its use by the observation of Celli and Guarnieri that the malarial parasites were stained while yet living by this substance. They found that in small doses quite a marked effect was obtained in several cases of intermittent fever. Since this time the drug has been used by a number of observers, most of whom agree in the conclusion that methylene blue possesses a well-marked anti-malarial action, the parasite often disappearing from the blood and the patient recovering after its administration. As an anti-malarial agent it is far below quinine in efficiency, while the parasite acquires, apparently, a certain tolerance to the drug after its continued use. In certain mild cases of the regularly intermittent fevers it may be given in doses of two grains every four hours in capsule, with possibly a curative effect. Larger doses have been given without ill effect—doses as high as 45 grains in the 24 hours. The only

unpleasant symptom following its use is, apparently, stran-
gury, which may be prevented by the administration of
small quantities of powdered nutmeg at the same time. After
the ingestion of methylene blue the urine has a deep blue
colour, and the fæces become blue on exposure to the air.
It is a remedy vastly inferior to quinine in this disease, and
many observers have reported satisfactory results from its
administration.

Phenocol.—This is an aromatic body, and a derivative
of phenacetin. The hydrochlorate or acetate has been much
used by the Italian observers for the treatment of malarial
fever, specially in the case of children, but with only moder-
ate success. It may be given in doses of 5 grains.

Other medicaments—The treatment of malarial fevers
has been from time to time attempted by other drugs than
those named above. Thus, iodine, strychnine, sulphur,
inunction of creasote with olive oil, arsenic, and alum, pre-
paration of eucalyptus, and helianthus have been recom-
mended. The value of these drugs, however, is slight,
except, as will presently be mentioned, in the case of arsenic,
which is often of service in anæmia and chronic malarial
cachexia.

Neem (*Azadirachta indica, Juss*).—It is an aromatic
bitter substance. The stems of the leaves of this tree are
greatly used in this country as decoction in fever. Another
substance which grows on the neem tree called *neem gurich*
or *glue* (*Tinospora cordifolia*) is a favourite remedy of the
oriental physicians for this disease.

Symptomatic treatment.—It is often advisable to
supplement the treatment with the specific remedy by certain
accessory and symptomatic measures. The value of purgation
has long been insisted upon ; and the old custom of begin-
ning the treatment of malarial fever by administering a
mercurial purge followed by saline is still believed in   It
may be of some worth in mentioning here that the experience

of the last epidemic of this country (India) has taught the practitioners that without purgation previous to administration of quinine, it fails to produce the desired effect instantaneously. It was unavoidably necessary to administer saline (magnesia, etc.) at first and then quinine which evidently proves remarkably very effectual to the patient. In cases where there are grave intestinal symptoms purgation must be avoided. Profuse vomiting or purging during a paroxysm should be controlled. Excitement and active delirium during the fever may also at' times require the use of bromide. Cold sponging, or ice bag on head or the actual cold bath may be of service in continued high fever, especially if delirium be present, or an hourly dose of quinine grain I and phenacetin or aspirin grain I which is the favourite method of practitioners of this country in controlling the paroxysms. In the collapse in pernicious fevers most active stimulation must at times be resorted to : alcohol, strychnine, and others may be freely administered hypodermically in the algid forms, external heat should be applied as well as enemata of warm water, or a cup of coffee. In comatose fever, it very often happens that the assistance of medical practitioners is called in when a patient is in a state of unconsciousness. In such a state the hypodermic injection of *quinine* and *digitalien* one after another have saved good many lives.

Treatment during convalescence.—It is the anæmia that is the most serious symptom that may require treatment during convalescence. In these cases iron and arsenic are our mainstays. In most instances iron alone either in the form of Blaud's pill or as the tincture of the perchloride in full doses, will be followed by good results. In severe cases arsenic may be resorted to : it is best given in the form of Fowler's solution. It is well to begin with small doses—minim 3—three times daily, after food, and to increase the dose steadily, one drop every other day, until the physiological effect is observed, slight suffusion

and injection of the conjunctivæ, gastro-intestinal symptoms, etc. The dose should then, after a few days' cessation, be reduced and maintained at the highest possible limit. Some very grave anæmias which closely resemble true pernicious anæmia, and react but little to iron, may show marked improvement after vigorous treatment with arsenic. It should be borne in mind that in rare cases arsenical neuritis may arise. Convalescence is frequently hastened by the exhibition of strychnine and bitter medicaments.

Treatment of malarial cachexia.—It is often a very difficult matter to treat chronic malarial *cachexia.* Active treatment by quinine will readily remove the parasite from the circulation and put an end to acute symptoms, but the extreme debility and the grave anæmia are often very obstinate. Owing to the great susceptibility of such patient to fresh infections or to a re-appearance of an old infection after the cessation of treatment by quinine, it is sometimes almost necessary to remove the sufferer to a non-malarious district. The anæmia, which is usually the gravest symptom, should be treated according to the suggestions given above. It is in these cases that persistent treatment of arsenic is specially valuable. The majority of cases of malarial cachexia owe their origin to the carelessness of the patient who fails to observe the ordinary prophylactic measures and does not carry out the proper treatment with quinine   The patient should be kept from all undue exertion : if the anæmia be very grave, fresh, hill and sea air are important   The diet should be most nourishing, and the patient should be allowed to sit in the open air, in the middle of the day if the climate be not too hot.   Bitter tonics are often valuable, particularly strychnine.   Most of the cases of this nature will recover, even in a malarious district, if treatment be properly carried out.   This leads to the question of especial treatment of relapses.

CHAPTER XIX.

TREATMENT OF RELAPSE AND ITS ASSOCIATING SYMPTOMS.

I have particularly and separately dealt with this question of recurring attacks of fever independently of malarial cachexia, because it seems to me to be of great interest, not only to the medical practitioners but also of vital importance to those who are engaged in dealing practically with the question of the prevention of malaria.

As some parts of India have been devastated, and the majority of the people devitalised by the pernicious influence of the malarial infection, it should be remembered that mortality at its initial stage is not very great ; the deaths attributed to it are mostly due to the persistence of frequent attacks, as proved by the loss of the many valuable lives of the young, the adult, and the old, who succumb to the continued effects of relapses of malaria. Besides, there are general complaints both on the part of practitioners, and patients, regarding its obstinacy to be eradicated, and after all it is our duty to save and protect the lives of our fellow-creatures as much as the limit of the science will allow.

Once the malarial parasites are lodged within the blood of a person and their timely eradication is not effected, malaria often becomes chronic, persons attacked with it harbouring the parasites for years afterwards. Further, a person with malarial parasites circulating within his blood may show no symptoms of the disease, and yet be the means of infection to others. Thus the question either of destroying all anopheles mosquitoes or of rendering all malarial patients innocuous, is a matter of great consequence and deliberation in the hygiene of malaria Christopher and Bently are quite justified in pointing out in their paper to the Bombay Medical Congress that human factor forms a soil far more

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suitable for the continued existence of malaria   They have discussed all points creditably in maintaining the arguments in its favour. The author's aim here is not to enter into its arguments, as this place is simply intended for indicating the means whereby to solve this obstruse problem.

The extermination of malarial mosquitoes is already treated in the previous chapter, and in connection therewith, it is only necessary to point out, that a certain procedure should be adopted to make the malarial patients free from producing any ill effects. To attain this object, it is most desirable to direct our keen attention towards the organs which are the source of mischief. It is an open secret, that *spleen* and *liver* have mostly to do with the recrudescence of this disease ; so naturally these organs claim our closest attention.

SPLEEN.

It is generally assumed in India that quinine relieves the fever only temporarily, and the notion indulged in by the people is that it is harmful rather than beneficial. These recurring cases of the so-called failures, evince the fact, that the drug is not judiciously administered during the attacks for want of proper discretion. It must be clearly understood that each attack of fever favours the tendency of the spleen to become larger and larger in its size, and the quinine which is administered at each interval, is hardly sufficient, both as regards the duration of its administration, and the quantity of its doses, to counteract its increasing growth. The efficiency of the prolonged treatment with quinine has not been sufficiently emphasised in the minds of general practitioners.

Naturally the question comes up to the front, how to prevent the recurrence of fever ? There ought to be some determining rule by which the period of *quinine-taking* might be reliably regulated, but, unfortunately, this problem has not attracted the attention of any author in text-books.

It has generally fallen under observation, that the longer the quinine is continued the smaller the size the spleen assumes, and at the same time the possibility of the recurrence of fever is reduced to a minimum. It has been observed in innumerable cases that neglect of the after-treatment of quinine results in recurrence of fever. Hence it is the duty of the physician to impress its importance upon the mind of the patients. It is necessary that they should also prescribe the length of time for which quinine-taking be continued. The guide to determine the duration of *quinine-taking* for ordinary purposes is the examination of the spleen,* the exact situation of which should carefully be ascertained, and be mapped out by *inspection*, *palpation*, *percussion* and *bi-manual* examination of the patient, both in the standing and the stooping postures. Undoubtedly it requires a considerable experience to correctly estimate its situation.

The general rule for the duration of *quinine-taking* is that it should be continued until the spleen comes to its normal position, and at the same time this makes it essential for the patients to undergo spleen test examination every week and later on every fortnight. Of course, the method and time depends upon the discretion of the attending physician, but the author's method of the administration of quinine follows:—

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* The spleen is situated deeply between the 9th and 11th ribs on the left side. It inclines posteriorly in close proximity to the spinal column and anteriorly does not extend beyond the mid-axillary line. It measures about five inches in length and three to four inches in breadth. The organ usually presents a notch on its anterior border, and its presence, under the palpation, beyond the arch of ribs is of great diagnostic value in case of the enlargement of the organ. On inspection the normal spleen cannot be seen, and on palpation it cannot be felt even in deep inspiration. It moves along with forced respiration, and when it is felt during that period it indicates enlargement of the organ and on percussion the dulness of the organ measures 3 inches in length, $2\frac{1}{2}$ inches in breadth, and percussion dulness does not quite reach the margin of the ribs, and if elicited it is a sure sign of the enlargement of the spleen.

The ordinary dose of quinine of 5 or 6 grains is to be taken twice a day for the first week after cessation of fever and then it is to be continued once a day for three weeks.

The treatment when the spleen is palpably enlarged, *i e.*, when it is entrenching beyond mid-axillary line and costal margin, is, that the quinine should be given twice a day for the first fortnight and once a day for another four weeks.

THE TREATMENT OF ENORMOUSLY ENLARGED SPLEEN.

Where the enlargement of the spleen has taken place with a permanent change in the form of fibrosis, it is hopeless to attempt to reduce it to its normal size, one has naturally to be disappointed in a radical reduction of the organ to its normal size. Patience and perseverance play a great part in the successful achievement of the result. The course of quinine is to be continued until the organ comes back to its original position, and along with this course a counter-irritant, like *Liqoure Epispasticus*, should be applied over the big tumour, the same procedure being repeated frequently until the tumour disappears from inside the arches of ribs.

The time for entire disappearance of the tumour in young persons is about three months, and in the case of the elderly people, may extend even up to six months.

RECURRENCE OF FEVER IN THE CASE OF CHILDREN WITH ENLARGED SPLEEN.

Often a failure in spite of quinine treatment for a continued period is brought to our notice, albeit, a failure, where no attention has been paid to the digestive and biliary functional activity. Besides intense anæmia generally occurs in children, and it is a matter of no surprise that quinine without *Hæmatinice* does not produce its effect. The author has found very efficacious combination of quinine dissolved in nitromuriatic acid with *Vin* Pepasine and Ferri. This combination has never deceived, and it has always proved extremely effectual.

LIVER.

The plea for introducing the subject of liver in connection with the recurring attacks of malaria, is that without its full consideration from a therapeutic point of view release from the tightening clutches of its relapses becomes next to impossible. It must be borne in mind that, like the spleen, the liver also becomes a victim to the enlargement during the accession of fever and under the influence of successive relapses, hepatic congestion gradually acquires more or less a permanent character. Moreover, the starting point of the onset of malarial attacks is the chilling of the already hyperemic or congested liver, such as may arise from a cold bath or a wetting, or from sleeping uncovered on a hot night under the canopy of heaven in a current of air. In tropical countries every resident is liable to be exposed to a variety of causes inseparable from the tropics, which give rise to circulatory changes within the liver. These may be referred to *malaria, heat* and *food.* The high thermal temperature acts as a stimulant to appetite and excites excessive loss of fluid by cutaneous transpiration creating thirst. There is an aptitude for over-indulgence in food and drink beyond safe *physiological limits*; besides heat makes persons prone to lethargy, making them shun active exercise. The importance of muscular activity lies in this that it promotes the activity of lung metabolism, that is, respiration, which does an important office in the combustion of the colouring matter of the bile which belongs to the group of carbon compounds.

Rich food is another very important cause which can readily be understood from the influence it exerts on the liver, as it receives from the portal vein all the liquid substances introduced into the digestive tube. Thus when the food is of too exciting a nature, and specially when a person has long been addicted to alcoholic drinks, such intemperance results in certain harmful consequences.

Injudicious personal habits are to be added to the above

causes. These include over-indulgence in rich food and over-stimulation with alcohol and deficiency of muscular exercise. All these circumstances tend to tax the liver to an unusual amount of physiological work. This over-stimulation of the organ to the abnormal activity corresponds to *Hypermias* of liver, that is the first stage of the *tropical liver*.

It is, in fact, a homage to the climate of India that these hypermias of liver are almost sure to occur, and it may be affirmed that there is hardly any individual European or Indian who does not suffer more or less from these hypermias

In order to verify this fact the livers of one thousand Indian labourers of ages ranging between 20 and 40, whose diet consisted simply of cereals. but who do enormous amount of manual labour were examined and found immune from malarial attacks and not even one of them presented a case of the hypermia of liver ; on the other hand, an examination of the same number of Indians, both Hindus and Mahomedans the standard of whose life varied according to their degree of civilisation, and whose diet differed from each other, showed that the livers of all these were in hypermic condition

The condition of hypermias is clinically evidenced sometimes by an increased flow of the bile giving rise to symptoms of diarrhœa of a bilious character, or by a deficiency of the bile causing constipation and by a highly acid urine evoking burning sensation after each micturation.

Such a condition of the liver owing to frequent attacks of fever advances a step further and passes into congestion, with blood stases,—that is, whenever there is blood accumulation in the liver it produces an increase in the size of the organ and a diminution of its functional activity. Monnert, who has made a careful study of hepatic congestion, has shown that the liver which in the normal state weighs about 1,600

grams may acquire, when forcibly injected into it with blood, a weight of more than 2,500 grams. This augmentation of weight manifests itself by an augmentation of its volume, and one of the first symptoms of congestive engorgement is a marked increase in the size of the organ ascertainable by physical signs.*

The active hyperemic condition of the liver may, even, under the influence of exciting causes, such as the rapid chilling of the body while perspiring, or the sudden suppression of perspiration by excessive drinking of cold water, and frequent attacks of malaria, pass into inflammation and suppuration.

But when the limits of hypermias are passed and the congestion of a pathological character sets in, the consequent arrest of the function gives rise to the following train of symptoms. There is first of all an increase in the size of the liver, an augmentation which effects the whole organ, then there is a pain on pressure which is never wanting. The lower border of the liver is felt through abdominal wall at the costal margins presenting hardness,—a consistency like leather. These congestions are accompanied by a fever which comes on between four and five o'clock in the afternoon and sometimes by an untimely attack of ague ; in fact the morning and evening temperature of such person is rarely equalised.

The patients affected with intense congestion of the liver complain of respiratory difficulty, such as *dyspnœa* and

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* The anatomical position of the liver shows that its superior surface lies in contact with the diaphragm reaching the level of the fourth inter-costal space. Its inferior border ends with the lower margin of the ribs except in the epigastrium where it crosses obliquely to the left. It is situated in the median line of the base of xiphoid in the mammary line of the sixth rib, in the axillary line at the eighth rib, and posteriorly at the tenth rib. Its exact position varies with respiration descending with the descent of the diaphragm and receding with its ascent. The edges of the enlarged organ extend beyond their normal situation.

dry hacking cough with a little or no expectoration. The most important symptom is present almost in all cases,— a slight jaundice characterized by a subicteric tint in the conjunctivæ. The stools are sometimes loose and blackish, and in some cases there are frequent evacuations of bowels in small quantities with mucoid and gelatinous material with fæces without tenesmus. In some cases there is diarrhœa of a pale watery, frothy, fermenting character. In most cases stools are *hard*, and *steel-coloured*, accompanied with troublesome intestinal *distension* presenting after meals, and it may be in some cases accompanied with even colicky pain.

The intestinal distension may be thus explained :—The utility of the bile from the digestive point of view is a well known phenomenon. The bile excites the peristaltic movements, clears the bowels, neutralizes the acidity of substances peptonized by the gastric juice, opposes to a great extent the fermentation of intestinal contents, and favours the digestion of fatty substances. Hence the phenomenon of intestinal distension is noticed, as the matter contained in the intestine is no longer kept aseptic by an adequate supply of healthy bile, therefore there is a bleaching of the fœcal matter which often has a horrible fœtid odour.

There are also a great many undefined symptoms arising from *auto-intoxication* from the intestine by the lodgment of fœcal matter specially in the lower bowels, namely, the *segmaid*, and *colon*. In these localities the fluid portion of intestinal contents becoming absorbed, gets hardened and so delayed in transit. Hence there is a chance of septic and putrid absorption rendering the reaction alkaline which is favourable to the development of *pathogenic germs*. Thus we see that constipation mostly concerns the sluggish bowels, and the retention of the fæces. Further, there is another painful complaint which is accompanied with these symptoms. It is piles which are almost sure to be present.

There is another affection of the digestive organs which is always attended with intense congestion of the liver. I refer to the dilatation of the stomach which gives rise to symptoms of gastric disturbance, such as heart-burn, eructation, flatulence, etc., etc.

In some cases the nervous phenomena, *e.g*, the atony of mental and digestive faculties also manifest themselves. For my part I am persuaded to explain that these symptoms ensue in prolonged cases. We should take much account of the penetration into the economy of putrid substances and of *ptomaines* absorbed from the surface of the intestine.

The existence of Hepatic insufficiency is also ascertainable by estimating the relation between the amount of bile in the urine and fæces : little bile in the fæces associated with abscence of *urobilin* from urine indicates hepatic inactivity of high degree; the absence of bile in the fæces accompanied with excess of *urobilin* in the urine means congestion of liver; normal amount of bile in the fæces with scanty bile in the urine is indicative of slight hepatic derangement. The presence of *Indican* in the urine, since normally it should be arrested in the liver, is of valuable sign of hepatic insufficiency.

In active congestion due to malaria recurring every now and then, though treated by quinine, the urine is of a highly yellow frothy nature with plenty of uric acid present in it. The colour of the urine of the condition passing into subacute or becoming chronic with congestive enlargement of the liver is blackish-brown, and on shaking it shows a yellowish tint, contains bile, and on standing forms a whitish-brown deposit. The colour of the urine in cases of very active congestion of liver, presenting the phenomenon of *pernicious* type of fever imperfectly controlled by quinine, or having had no quinine treatment at all, and as the time goes on lapsing into a continued fever with a difference only in morning

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and evening temperatures, accompanied with other severe symptoms, is diluted port-wine, frothy, that may be mistaken at first sight for Hæmaturia. The same urine is scant in quantity, and on standing in a glass vessel lays a sediment of *whitish-grey* colour ; further on heating in a test tube the same urine becomes turbid. The examination reveals hyaline casts, and brownish granular material, but no blood corpuscles The urine contains an excess of uric acid, in some samples bile pigment is present, in others none.

This characteristic feature of the urine may be represented by *Hæmoglobinuric* fever which is asserted to be a distinct disease of a dangerous type. It would not be out of place here again to allude to the question of Haemoglobinuria in connection with congestion of the liver. Such conditions are not rare in the experience of those medical practitioners who practise amongst Indians, but in fact these cases, *i.e.*, ill-treated malaria, as a rule, come before us in numbers, as the majority of people having an abhorrence for quinine prefer a mode of treatment other than medical, in the initial stage of malarial attack. When the condition of these patients gets worse they come to us affording a facility for making an observation It is noticed that those who have had pernicious attacks of malaria and have developed in the course of time a good many symptoms indicative of liver complaints with the special character of urine as a rule, they do get better under the ordinary régime of treatment which will be described later on, It has been observed that cases have begun primarily as a grave type of fever eliciting *malignant parasite* on examination, and the same acquire in the course of time say, within two or three months, according to the severity of the case, symptoms o the hæmoglobinuric fever. The cases of such descriptions were collected for the purpose of observations and all these cases pointed out the history of liver affection previous to malarial attacks ; while the observations were continued on

hose ill-treated cases which presented no ascertainable
iistory of congestion of liver prior to the attacks of pernici-
ius type of fever, thus they did not depict such phenomenon
o be assigned a distinct type of hæmoglobinuric fever.

It might be of some interest in reproducing here the
·eport of the urine of a distinguished patient who was under
ny observation, from start to finish, bearing a similarity to
he above-mentioned circumstances. This patient, prior to
nalarial attack, was for a time subject to liver complaints.
During the course of his illness monthly examinations of his
ilood and urine were carried on ; and it was noticed that
gradually his urine attained the appearance represented in the
·eport. I may add here that this patient got a surprisingly
ininterrupted and quick recovery by the treatment of hepatic
congestion with morning doses of quinine.

The urine was carefully analysed in a chemical labora-
tory by an expert in my presence.

TRUE COPY OF THE REPORT.

I.—PHYSICAL CHARACTERS.

Specific gravity	...	1022·1.
Colour ...	...	Deep red.
Odour ...	...	Strong garlic odour.
Appearance	...	Turbid due to suspension of cloudy and mealy masses.
Deposit ...	...	Small amount of whitish-grey sediment which slowly increased in quantity in course of time.
Quantity sent	...	38 fluid ounces, probably passed in 24 hours.
Total solid	...	44·2 grains per 1,000 grains of urine.

II.—CHEMICAL CHARACTERS.

Reaction ...	...	Very faintly acid or neutral.
Albumen ...	...	Slight.
Sugar ...	...	*Nil.*

Excess of phosphates   ...   2·8 grains of phosphoric acid per fluid ounces of urine.

Excess of oxalates   ...   ·108 grains of oxalic acid per fluid ounce of urine.

Excess of urates   ...   ·77 grains of uric acid per fluid ounce of urine ; almost five times the normal quantity present.

Bile   ...   ...   *Nil*

Blood   ..   ...   *Nil.*

Fat   ...   ...   *Nil.*

Pus   ..   ...   *Nil.*

III — MICROSCOPICAL CHARACTERS.

Blood corpuscles   ...   *Nil.*

Pus cells   ..   ..   A few cells like that of pus cells found out ? Gonococci.

Tube casts   ...   A few resembling granular and hyaline casts found present.

Renal epithelium   ...   Not found out.

Epithelium from bladder   Some epithelial cells were found out in the sediment.

Uric acid crystals   ...   Plenty of these found present.

Amorphous urates   ...   Some found present.

Crystalline urates   ..   *Nil.*

Amorphous phosphate of   *Nil.*
 lime.

Crystals of phosphate of   Some found out in the sediment.
 lime.

Crystals of triple phos-   A few found out.
 phates.

Crystals of oxalate of   Some found out.
 lime.

Spermatozoa   ...   *Nil.*

Excess of squamous epi-   *Nil.*
 thelium.

Excess of mucus   ...   Some found present.
Bacteria   ...   ...   Plenty.
Torula   cells or   yæst   *Nil.*
  cells.

NOTE :—There was a large excess of brick-dust coloured minute particles of uric acid. There were some black or opaque roundish spots present.

The clinical and therapeutical observations lead us to hold the view that Hæmoglobinuria is a mere aggravated symptom of ill-treated malaria of a malignant variety. This condition is not observed in simple or mild variety, for whatever time it may be left untreated. As the destruction of the red corpuscles very likely is not so great in this variety of fever as in the malignant type, it is obvious that repeated and persistent blood destruction bring about such a change in the condition of the urine   Such circumstances, however, lead one to believe that Hæmoglobinuric phenomenon only occurs in malignant form of malaria owing to its frequent attacks, and being uncontrolled by quinine, and then in such cases only as a result of the congestion of liver previously present.   The congestion of liver, in my opinion, would appear to be a necessary condition for its production, as the liver in malignant variety becomes more highly congested, and its power to deal with destroyed red corpuscles impaired ; consequently the hæmoglobin is thrown out with urine giving rise to that condition of urine.   In other words, the augmentation of already congested liver due to frequent attacks of pernicious type of fever incapacitates the liver to deal with hæmoglobin.

Another possible explanation of the manifestation of Hæmoglobinuria may likely be offered from the facts that all the blood-forming glands (bone-marrow, spleen and liver) being malignantly attacked by malaria as its evil effects upon them, lose their power of activity, and the continuous and persisting destructive process of malignant parasites in the red corpuscles, at the same time, causes attenuation

or loss of the power of resistance ; all combined together collectively result in the solution of red cells.

All these are of course hypotheses, but they may serve the purpose of indicating in a very broad and general line that Hæmoglobinuria is malarial in origin.

Here again I would like to refer to in connection with this affection, as I do not agree with the view that quinine in any form is instrumental in the production of Hæmoglobinuria. This drug may be harmful in other tropical countries, but it is not so in India where the occurrences of cases are so numerous, that generally we rely upon quinine, and have not noticed any harm resulting from its use in any case, but of course it is administered along with the treatment of hepatic congestion. I would like to add that I have found *quinine Lactate*, and *Salicylate*, and *Litheum Benzoite* most useful in bringing about successful results.

Such are, in brief, the principal symptoms noticed in persons who are subject to liver complaints, who had had previously malarial attack, and had it continued ever and anon. Now I proceed to the treatment of these symptoms.

The treatment depends on whether the patient is cachectic or plethoric in physique, and it is only after a careful study of each individual case that medication suitable to each case can be adopted. The treatment may be grouped under the headings of Medicine, Diet, Habits, and Clothing.

Medicinal.—Over and above all administration of quinine as a routine treatment dealt in spleenic enlargement must necessarily be given halting anchor. Other measures must be co-associated with it in order to combat a variety of symptoms without which desired effect would be unattainable.

The value of purgatives in these cases, especially, in connection with *auto-intoxication*, can not be over-estimated. In forming our conclusions we are assisted by nature which sometimes effects a cure in cases of hepatic congestion by the establishment of diarrhœa. In treating such cases we

cannot do better than imitate nature, and even supplement her efforts. The class of purgatives found useful in these cases are the following salines :—

1. Magnesia suplhas (in large doses).
2. Sodii sulphas.
3. Sodii phosphas.
4. Carlsbad salt.

The best way to administer a purgative is to give a small dose of calomel at bed-time followed by the saline early in the morning. This régime of treatment produces marvellous results in persons having a tendency to hepatic congestion.

As for chronic or subacute congestion of the liver originating in injudicious habits and diet accompanied by frequent attacks of malaria greatest reliance can be placed on the following measures to effect a rapid cure :—

Local Application.

1. A large blister has a marked resolvent action in intense congestion with enormous enlargement of the organ. I have always derived excellent results with the application of *Liqr. Epispasticus* over costal margins.

2 Local blood-lettings have also been advised for congestion of the liver. Apply over the hepatic region, where the pain is very severe, a dozen leeches. Leeches may also be applied not over the liver but over the anus. But this spoliative method is to be reserved for plethoric persons and those in whom the hepatic congestion manifests itself by very acute symptoms ; for, in general, I am not a strenuous advocate of blood-lettings in disease of the liver. These withdrawals of blood almost always entail perturbation which manifest themselves by hœmorrhages, so frequently observed in hepatic affections.

3. Counter-irritants over the liver, such as mustard plaster, *Liniment. iodin.* and *Liniment. crotonis* and *Ung. hydrarg. Oxide rubri* are found very useful.

For internal medication preference should be given to Chologogeus, for example, *Euonymin* and *Podophyline.* As for myself I highly prefer the B. P. Tincture of these drugs in small doses along with other medicaments corresponding to the symptoms. Another drug, which is very commonly used in this country for this disease, is *Ammonium chloride* in a dose from 5 to 10 grains. I can testify to its value in slight cases of hepatic congestion as very effectual. This drug acts in diminishing the congestion of the portal system by augmenting the urinary secretion and by acting as a laxative and causing diaphoresis.

Especially in cases of hypermic condition of the liver I cannot sufficiently emphasise the efficacy of mineral salts, such as *Vichy, Carlsbad* and *Bubinat,* which owe their activity principally to Sodium sulphate. One of these salts is to be taken early every morning. In my opinion Vichy beats the rest of its kind.

Another drug, which is very commonly used in India, is *Chiretta.* In cases of malarial cachexia with the affection of the liver and the spleen, this drug proves very effectual. I can attest its worth in such cases as a special tonic. Probably it acts as a hæmatinic by removing the obvious cause of the deficiency in hæmoglobin or anæmia which is noticed in cachexia. It not only increases the amount of hæmoglobin when these are deficient in the corpuscles, but, also the number of red corpuscles, consequently patients under the effect of this drug begin to have red colour in their cheeks. Other properties of this drug, as far as ascertainable, are that it acts as stomachic and chologague. It is a favourite drug for such cases, and I prefer an infusion freshly prepared. I have prescribed it in such form in thousands of cases, and it has never proved a failure ; its action is much aided by good food and exercise in the open air.

There are certain drugs which have a great reputation amongst *Hakeems* in India as especial remedy in live disease, namely :—

(1) *Gokhrū*—Technically known, *Tribulus terrestris* Linum, belonging to the family of Zygophylleæ.

(2) *Kāsni*—Technically known as *Cichorium Intybus* Linum, belonging to the natural order Compositiæ.

The infusion of these herbs is used, and they act not only on the liver but also on the kidneys, and it is probably due to enhanced diuresis that they act indirectly on the hepatic diseases.

In most advanced cases we especially want to combat the symptoms arising from *gastric disturbance* and *intestinal putridity* which result from the absence of the bile in the intestine. The indication of the treatment of these must comprise two main objects, namely :—

(I) To combat *hyperacidity*.

(II) To check *fermentative* process. For this, it is necessary to keep four objects in view, *viz.*—(*a*) to moderate the *microbial milium* of the intestine ; (*b*) to combat the *putrefactive* action of the Bacillus coli in the large intestine ; (*c*) to excite the evacuation of *putrefactive* products from the large intestine, and lastly, (*d*) to combat the symptoms of colitis.

For the first group we employ *Sodii bicarbonas*, and *hydrated* or *calcined Magnesia* and *Lethii carb ;* for the second we have to combat the various phenomena as mentioned above. For (*a*) we excite the secretion of the bile, as it is an antiseptic agent of the first order ; for (*b*) we make use of the drugs, such as *Salol, Resorcine, vegetable charcoal* and *Benzo-naphthol* ; for (*c*) we can prescribe powder of *rhubarb,* and for (*d*) *Salicylate* of *Bismuth* and *pulv. accacia* and *phenalegine* or *papine.* I prefer powder of these drugs to be given a short time after meals with Vichy water.

Last but not least ranks the use of *Nux Vomica* in these cases. The effectual value of this drug becomes known to the patients themselves after a few doses and they begin to thank Providence for its mercy in extricating them from the jaws of death.

For respiratory troubles *Ammonium carbonate* and *Coffine citras* should be used. They act like a charm.

Besides the mineral waters mentioned above, a heroic remedy, *viz.*, Hydrotherophy,* is placed on a high level in France, for the treatment of active congestion of the liver brought about by injudicious habits and malarial poisoning. It was Fleury who first pointed out the benefit which can be derived from the employment of the *cold douche.* How ought this douche to be administered ? The cold jet douche is applied over the liver in order that the action may be more local. Place the patient in such a position that with the right arm slightly raised, the thigh of the same side half bent, he may be able to receive over the hepatic region the jet of the cold water. The duration of the douche should be very short. It should not exceed thirty seconds and generally fifteen seconds will do. There is another form of the douche called *Scotch* or alternating, *i.e.*, the douche in which during a space of a minute the cold douche and the warm douche are applied alternately. Lastly, when the patient gives sign of too great nervous irritability, when, instead of ameliorating the condition of the liver, these douches augment the volume of the organ, we should employ the *Swan's neck* douche which throws along vertebral column a considerable volume of water, but at low pressure.

Such are the most common and salient therapeutic measures to be adopted in this affection. Next to the medicinal agency the *dietic* treatment may be put almost at the

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* Prof. Dugardin Beaumetz.

same level. As regards the diet care should be taken that the patient does not eat those substances which give rise to too active fermentation in the intestine. The diet which is low in proteid on account of its deficiency has the tendency of *fermentation* in the bowels and this offers an additional field for the growth of Bacteria.

As a rule, Indian diet is very palatable, but at the same time it is very indigestible and unwholesome having the property of producing intestinal putridity. As in a great number of cases active congestions of the liver have for their cause too abundant and too stimulating a diet, so it is indispensably essential to regulate even to the minutest particular the alimentary regime of patients and to prohibit all substances which cause congestion, such as too highly seasoned foods, too generous wine and too abundant meals. With regards to fatty foods my advice is to take them very moderately, and I may, above all, insist upon vegetable and starchy rather than animal food ; vegetable and legumes are almost all permissible and should form a part of every day's fare ; as regards bread prepared in the Indian kitchen (chapati), a moderate use of it ought to be made, crusted bread being preferable. The bread should be prepared from very coarse wheaten flour and be very fine. All kinds of pastries and sweets should be avoided. Animal food may be permitted but with moderation. In fact in severe cases it should be cut off from the dietary altogether and there should be entire abstinence from eggs. Preference may be given to young fowls, wild and aquatic birds and fishes over beef and mutton. As regards milk diet in the treatment of the congestion of the liver, it has been considered by some authorities as favourable by others as injurious. At any rate, most of the Indians have got a disgust for milk, and some would go even so far as not to take it under any circumstances. However, before ordering milk diet it must be ascertained whether there does exist or not any dilatation of the stomach. In case where the

stomach is dilated an exclusive milk diet should not be permitted. Care should also be taken not to allow too much fluid or cold water drink during food, it may be taken after finishing the meals, and it is much better to drink water a little while after. A great deal has been spoken about the nutritious value of ' Sanatogen.' I may add that it is very valuable in these cases, and undoubtedly it aids in the buildng up of lost tissue.

All the fruits may be freely partaken of, such as peaches, bananas, strawberries, prunes, figs, grapes, oranges, apples, etc., etc., but almonds, nuts and very sweet fruits, like mango, in moderate quantities only.

I now pass on to the regulation of the habits of patients. They must not cultivate sedentary habit or remain in bed too long. They must not take cold baths. They must not also take cold drinks too frequently, nor sleep at night in the open air, nor expose themselves to cold in any form. They must clothe themselves warmly and shun alcohol in any form. They should not sit or loaf about in wet or damp clothes ; they should change at once when they come in wet with rain or sweat ; they should not get cool in wet clothings or lie down half naked. They should under all circumstances keep the stomach covered and take care that the covering does not come off in sleep during night. Exercise should be taken twice a day or at least once in twenty-fours hours, and it should be of such a character as to provoke perspiration. When a patient is in a convalescent state we recommend friction of the skin, cold effusions, warm salt baths, vigorous exercise in the *open air*, *sea air* and lastly, *hill air*. Journey and change of scene will do much to revive the drooping spirits of patients who feel very much depressed. By acting upon such an advice the patient's attention will be diverted from constant brooding over his disease and gloom, which has cast a veil over his reason and induces his mind to feed upon unnatural fancies.

When patients are continually suffering from liver complaints they should be advised to leave the tropics for a time. " Nothing relieves these cases of chronic congestion so quickly or so effectually as a resort to the Carlsbad cure." In case of those who are unable to proceed to Carlsbad, the usual precautions with regard to habits, clothing, diet, catching chills, and taking drinks are to be very carefully observed; and lastly, a weekly saline purgative should be the means of keeping up the balance of health in the tropics.

Our guide to indicate a complete cure of these hepatic complaints is the colour of the urine and fæces. The treatment is to be continued until they attain their normal colour.

A few words about the last measure of the treatment, that is, the *clothing* of those persons who are constantly subject to hepatic complaints in the tropics. The external temperature has a great influence over a person's circulation of blood. It has been pointed out in the previous pages that the congestion of the liver is caused by circulatory changes within the liver, and that the clothing suitable to the climate is the means of maintaining a uniform circulation. The clothing must, therefore, be necessarily adopted to the nature of the climate. Since the patients cannot get the climate to accommodate itself to them, they must endeavour to accommodate themselves to it. It is important to bear in mind that it should be of such texture that the bad effects of great and sudden changes of temperature are warded off.

The general effects of a change in bodily temperature may briefly be mentioned here. If the bodily temperature suddenly undergoes a change, *i e.*, from hot to cold, the action of the skin stops, and it becomes cold while a large amount of blood rushes to the internal organs resulting in congestion. It is an essential point in the regulation of bodily temperature that the skin should be kept warm, therefore next to skin wearing a warm clothing is of vital importance. In India during hot months woollen clothing is

unbearable, but unavoidably necessary for these patients. For these reasons I find an under-clothing prepared of a mixed fabric of wool and silk to serve the purpose. The cotton clothing, when damp, is dangerous, and it is one of the sources of chills.

All that the climate of India requires to ensure perfect health is a suitable modification of the habits and customs. It is an old saying that " prevention is better than cure," and it is the foundation on which all the hygiene or laws regarding health, are based. " He who takes to attend to these laws is more likely to preserve his health than he who does not care for any of these things." It is necessary for all practical purposes that a man should have some general knowledge of the prevention of disease and for guidance in the management of his own health, that he may be able to exercise " a reasonable care, thought and prudence", which is a matter of such importance, that every one is bound to admit. Many Europeans arrive in India with the mistaken notion that precisely the same habits and mode of living as they have been accustomed to at home can be continued here with impunity, with the result that they fall a victim to liver complaints and very often are obliged to return to Europe.

CHAPTER XX.

CLINICAL OBSERVATIONS.

CASE 1.—This patient was a professional person, who suffered in the autumn from a prolonged attack of tertian fever which reduced him to rather a cachetic condition. Recovery followed full doses of quinine within a week. For nearly three months after this his health was perfectly good, the patient living in non-malarious districts. One afternoon during the hottest time of the year, while making a pedestrian tour, after a prolonged walk, during which the patient was subjected to great changes of temperature, there was a well-defined and characteristic malarial paroxysm. The true nature of the attack was not suspected, but on the third day, at the same hour, while travelling in a railway-carriage, there was a second paroxysm. He consulted me; treatment with quinine was begun, continuing for six weeks, which resulted in the immediate and permanent disappearance of the paroxysms

CASE 2.—This patient was a very powerful person, 38 years of age, who was seized about 2 P M with slight chilliness, very severe pain in the left side of the chest, dyspnœa and a dry cough. Towards 8 A.M., while the malarial symptoms were present in the highest degree, there was discovered a distinct rough friction sound, the temperature being moderately elevated and the skin hot. He suffered from Malaria six months ago. Wet cups, counter-irritants and opiates were ordered, and the next morning the patient was free from pain and all tendency to cough, there being nothing abnormal discoverable on auscultation. At twelve o'clock that night, however, the attack was repeated. At nine in the morning the same symptoms were seen as two days before, although in greater intensity, and the friction sound was not only more plain but more widely extended. At four o'clock in the afternoon the patient was found in perspiration, and as he was almost free from fever and from pain, and as he was feeling well again the next morning, doses of quinine with other medicines were prescribed, and his cure was immediate and permanent on ordinary course of treatment.

CASE 3.—M. S., aged 55, suffered from Malarial attack one month ago and had been under Hakeem's treatment all the time. One day he complained of some unusual symptoms attending a chill. He was found in a stupor, from which he was with difficulty aroused sufficiently to swallow a dose of quinine. His face was pallid and inexpressive; the skin was cool and moist; the extremities were shrunken and cold, the pulse was small, easily compressed by pressure, and irregular, the tongue

was large and moist; and the pupils were somewhat dilated. He was again visited an hour and a half later, and found to be in a deep stupor. The surface of the body was cold; the extremities and face were shrunken and blue; the pulse was barely perceptible, and large, liquid and offensive stools occasionally escaped from the bowels without the consciousness of the patient. This form of pernicious malarial fever was the cause of his death about three o'clock in the afternoon.

CASE 4.—This case was of the same nature as the foregoing one and the patient was an unmarried female, living in a malarious district, who complained one afternoon of great cerebral fulness and unaccountable sleepiness and debility. She retired to her room, and after a few hours' sleep resumed her household occupations. The next day similar symptoms manifested themselves, but earlier in the day. She again slept for some hours, but complained of great prostration after the sleep. The next day, about 10 A.M., she complained of a return of the stupor, and while returning to her room requested that she again be visited if she did not awake in a better condition. At 1 P.M., she was found profoundly comatose, with cold extremities and the surface bathed in perspiration. She received injections of Degitalien in one arm and quinine in other; a few hours afterwards she regained to consciousness. The ordinary treatment by the mouth was followed until the patient fully recovered.

CASE 5.—C. L., a clerk, was seen in an insensible condition one afternoon during the season of greatest malarial prevalence. The temperature at the time was 105·8° F., pulse 120, respiration 40, and he was able to swallow liquids placed far back in his mouth. He was ordered quinine in solution, ten grains to be given every fourth hour. The next day it was found that the patient had taken and retained all the quinine ordered; he was perspiring profusely; his temperature was 97·8° F; he was more conscious; and he was able to take food and water when offered him. He was at once given a purgative, and cooling drinks were prescribed. In the evening the temperature was 99·3° F., the next day normal, and the patient forthwith entered upon a satisfactory and uninterrupted convalescence.

CASE 6—This patient was also comatose and entirely insensible when first seen. He was treated by large doses of quinine in solution per rectum, and by calomel gr. vi and bicarbonate of soda gr. xx placed upon the base of the tongue, and caused to be swallowed by a tablespoonful of water trickling over the powder. As the patient began to recover, it was noticed that his right arm was paralysed. A history, subsequently attained, showed that the patient was an overseer, and had been engaged in making some land surveys in a swampy district, and had often been obliged to swim across the ponds and to sleep at night in the open air, sometimes without any protection from the weather. He had previously enjoyed good

health, and was altogether unable to account for the paralysis of his arm.
During convalescence he was treated with iron, strychnine, and preparations of cinchona, and by cold douches and frictions to the paralysed arms.
He made a slow, but satisfactory, recovery in some length of time.

CASE 7.—C E., age 26 years, said that for over a year he had been
working in an intensely malarial district, preparing the bed of a railroad,
that he had malarial diseases for several months, and had suffered a severe
chill the day before being seen. A few hours afterwards his temperature was
103°F., his pulse 120, and his respirations 29. There was effusion present
in both thoracic cavities, and very marked dropsy of the abdominal cavity ;
the lower lobe of the right lung was œdematous, the legs were anasarcous,
pitting greatly on pressure, with several ulcers of long standing. The urine
was loaded with albumen, and showed under the microscope abundant
blood-corpuscles. There was considerable jaundice present, which the
patient states to have occurred suddenly. He was ordered five grains each
of calomel and bicarbonate of soda bed time, to be followed saline in the
morning, after movement of the bowels with ten grains of quinine in
solution every two hours. In four days' time the patient had taken and
retained one hundred and eight grains of quinine , the secretion of urine
was abundant; there was no blood present and only a trace of albumin ; he
was ordered twenty drops of the tincture of the perchloride of iron three
times daily. The above comprises the whole treatment in this case of
hæmorrhagic malarial fever, except one important measure, which consisted
in determined and persistent efforts at forced nutritive meat essences,
milk, or eggs, they were given as persistently as drugs. The entire
illness did not last longer than four weeks, and the outcome thereof was
entirely satisfactory.

CASE 8. –H. K., aged 50, had a history of malarial poisoning for
several months ; was considerably jaundiced when he came first under obser-
vation, and suffered from anasarca in the legs. He had been patient of liver
complaints for a long time. Under the administration of a laxative, followed
by quinine he improved so greatly, that he was considered cured within a
week. Three weeks later, at 1: A.M., he had a chill which lasted several
hours ; this was followed by violent fever with a rapid and compressible
pulse, much jactitation, incessant vomiting of a greenish-black fluid, urine
red with greyish-white sediment, and the sudden supervention of intense
jaundice. The secretion of urine ceased on the morning of the next day,
and he died at 11 o'clock the same evening.

CASE 9.—The clinical history of J L., aged 30 years, will serve to
illustrate the course of a case of the so-called typho-malarial fever. He was
first seen on the evening of December 10th. He had been ill for some days
with ague. Ten grains of quinine in solution, with fifteen minims of the
tincture of opium, were administered forthwith, and again the next day. On
December 13th there was tenderness and gurgling in the ileo-cæcal region ;

epistaxis, rose-spots on the abdomen ; but there had been no stools since the 11th. He was ordered a teaspoonful in water, of a mixture of dilute sulphuric acid, syrup of orange, and tincture of cinchona; and also beef-essence, milk-punch, and milk. On December 13th, two very offensive liquid stools ; ataxia greater ; skin yellow and countenance dull and listless. December 14th, fresh rose-spots ; tongue dry and brown ; three stools ; much jactitation. December 15th, more ataxia ; some delirium ; pulse, 100, weak Given two and a half grains of quinine in solution with three minims of the tincture of opium, every two hours. December 16th, pulse 128, week ; delirious. December 17th, new rose-spots ; abdomen tympanitic ; tongue brown, dry ; sordes on teeth and lips ; eyes indented ; very delirious. Treatment continued ; nutrition and stimulants given methodically. From 17th to 22nd, but little change in condition and treatment. December 22nd, coma vigil ; completely delirious. Prescribed a tablespoonful, every three hours, of a mixture of the sulphate of morphia and tincture of digitalis (of each three drachms), the nitrous spirits of ether (two drachms), and the solution of citrate of potassium (three ounces). As the oscillations of the temperature became more marked, quinine was resorted to, apparently with good effect. By the 8th of February the patient was considered completely recovered. It should be noted that after the 14th of December the patient's bowels were rather constipated, and the stools occasionally moulded and very dark in colour On the forty-fifth day after coming under observation, the patient had a severe chill, followed by a rise of temperature to 104° F. This yielded to full doses of quinine. This was a typical instance of so called typho-mala-rial fever. The blended symptoms, as well as those special to each disease, are sufficiently exhibited by the rose-spots and the marked nervous symptoms. In so far as signs of intestinal lesions were manifest, the typhoid process seems to have been unusually mild.

CASE 10.—This patient, a male who had just attained his manhood appears to have suffered from fever with relapses since August. In the latter days of October he had slight vertigo, weakness, and an impediment in walking. On November 13th, he was observed to be suffering from increased vertigo and headache. His speech was slow and scanning, he had nystagmus, a tremulous tongue, volitional tremor, and inability to walk without support, and was seriously anæmic ; the temperature was normal. As all of these symptoms continued, and the patient's condition kept getting worse, the blood was examined, and the presence of the *æstivo-autumnal* parasite was discovered. All the nervous symptoms disappeared and the illness was speedily cured under the exhibition of quinine and arsenic for eight weeks and since then he was never troubled with it again.

CASE 11.—A patient of the same age as the foregoing, during a relapse which occurred in the month of October (16th), had vomiting and vertigo. On November 8th, the same symptoms re-appeared. On the 9th he found articulation difficult, speech being slow and scanning ; there was

great weakness of the lower limbs, a vacillating gait with a tendency to fall forward, exaggeration of the tendon reflexes, ataxia of the upper limbs, volitional tremor, slow pupillary reflexes, and slight nystagmus, but normal sensibility. On the following day the symptoms were all more marked ; the vomiting was incoercible and rendered rectal alimentation necessary ; there were extreme weakness, apathy, a feeble voice, complete muscular relaxa· tion, increased dysarthria, vertigo, no matter what position was taken by the patient, and progressive anæmia --all of which gave the disease an appearance of the greatest gravity. Although the temperature was normal for several days, an examination of the blood was made, and æstivo-autumnal parasites were found. The stimulant and specific treatment which was then immediately resorted to for several days following, brought about an improvement in the condition, which, on the 15th, was very marked in spite of the persistence in the blood of amœboid and crescent parasites. An ophthalmoscopic examination showed retinal hæmorrhages. On the 18th, there were only crescent forms, but these in increased number. The improvement was rapid, but the nervous symptoms disappeared slowly. On December 13th, the patient discontinued treatment, being in good condition, with only slight dysarthria. On December 31st, he again came under observation with fever, anæmia, and a cyndrome similar to the one just described. In the blood there were æstivo-autumnal amœbæ and crescent bodies. When the fever dropped the hypodermic injections of quinine (gr. viii per diem) were continued, and there were diminished nervous symptoms and apyrexia until January 12th, when there was a slight attack with a temperature of 100° F. On January 15th, 16th, 17th, and 18th there were quotidian febrile attacks, with high temperature, parasites in the blood, and exacerbation of the nervous symptoms. After eight days of apyrexia, there was a return of three quotidian attacks, in spite of the continued use of small doses of quinine. Careful dieting being superintended and the dose of the drug increased, the fever and nervous manifestations entirely disappeared, and he made complete recovery in seven weeks.

CASE 12.—The patient was a youth, aged 19, who was presented for treatment of a grave fever, the nature of which was unrecognised during the first week. For several days the fever continued to be irregularly intermittent or remittent, and was prolonged for about twenty days with brief interruptions, accompanied by vomiting, diarrhœa, splenic tumour, and dulness of the sensorium. During the fever the anæmia became very grave, and special nervous symptoms arose, consisting in clonic movements and abrupt and rapid rhythmical jerkings of the muscles of the shoulder, neck, face, and eyes. An examination of the blood, upon a day in which the patient's condition was most serious, showed the presence of æstivoautumnal parasites, and revealed the real nature of the disease. Prompt specific treatment caused cessation of the fever, but not of the symptoms of motor irritation, to which was superadded a muscular weakness so great

tnat the patient could not lift his head from the pillow nor move his body.
The muscles became rapidly atrophied without showing any qualitative
alteiation in their reaction to electricity, but merely a diminution in the
galvanic and faradic excitability. At the same time the patient was in a
state of mental confusion, with agitation and hallucinations, especially at
night ; following this he had apop'ectiform and epileptiform attacks which
resolved without a tiace being left. After his illness had lasted about a
month, the general condition began to be bettered, as was also sanguini-
fication, and improvement in the nervous symptoms followed. A few
relapses of the malarial fever, which were of no great severity, interrupted
the course of recovery for about a month and a half. But these were
overcome with the salts of quinine, and the patient advanced rapidly
to convalescence. The blood showed the alterations of ordinary anæmia
following malaria, and the parasites found in the blood, both in the original
infection and in the relapses, were the æstivo-autumnal. The patient was
completely restored to health after about three months of sickness, *i e.,* by
the beginning of January.

CASE 13.—This patient was an agriculturist, just turned manhood,
who contracted the fever in August, and had relapses up to the 5th of
December. On that day, during the febrile attack, choreic symptoms began
and continued with increasing severity for several days, unaccompanied by
fever, and in spite of the administration of quinine, and became so troublesome
as to prevent his working and obliged him to seek medical advice. On
examination, his condition was the following : malnutrition, pallor, splenic
tumour, in the blood a few crescent bodies, nystagmus of an irregular and
abrupt nature, with intercurrent strabismus and rotation of the eyeballs,
increased under fixation ; rapid, brisk, and disordered movements of the
orbicular muscles and of those of the face and the neck, especially on the left
side ; rapid and rhythmical clonic movements of the tongue causing dysar-
thria ; very active cutaneous reflexes ; marked depression and somnolence.
On the following days, the apyrexia continued and the crescent bodies having
disappeared, theie was atrophy of the muscles of the neck, trunk, and limbs,
the patient being unable to sit up in bed ; the appetite was voracious, and
there were long peiiods of sleep. From the 21st of December there was
improvement ; the patient could sit up in bed, but if he attemnted to get up
he was seized with violent clonic contractions of the muscles of the trunk
and limbs. By the middle of January there was great improvement ; the
patient walked with long and bounding steps; the dysarthria had disappeared ;
nutrition had improved ; the nystagmus occuired only after fixation ; the
appetite continued to be voiacious, that is, there was a tiue boulimia.
He appeared to be completely cuied in two months' time.

CASE 14.—This patient, a man of 25 years, died in a condition of
coma the same day as he was first seen. In the blood were found small
amœboid parasites, pigmented leucocytes, nucleated red cells, and parasite

infected and melaniferous endothelium ; before coming to my inspection the patient was observed by a medical man who had diagnosed it as a plague case.

CASE 15.—This patient, who had been cachectic for nearly a year, and all through had been under *Hakeem's* treatment for liver complaints. On the morning of March 22nd, he had an attack of hæmoglobinuria ; he took a dose of quinine after great persuasion ; while he began to recover the treatment was abandoned On March 31st, there was another attack of fever which lasted until the 7th of April, with daily elevation of temperature to 104° F. ; phenocoll was given without result On May 7th, quinine was injected hypodermically, causing cessation of the fever. On May 25th, not feeling well, he took a dose of quinine as a precautionary measure. He died in three hours from an attack of hæmoglobinuria, that is, from complete suppression of urine. As the treatment being very irregular which caused him death.

CASE 16.—This patient was a cachectic person who had suffered from malarial fever many times, and also had suffered from congestion of liver previous to attacks. During the last relapse, after the fifth day of fever, hæmoglobinuria appeared and lasted a little more than twenty-four hours : the patient had not previously taken quinine. During the attack malignant parasites were found in the blood of the finger. He was put on ordinary routine treatment. All complaints subsided finally in the course of time.

CASE 17.—A youth of 20 years had fever in the month of June, followed by many relapses. The last attacks occurred on November 16th and 17th. On November 21st he was seized with fever accompanied by chills and vomiting. and later by diarrhœa ; he passed urine of a blood colour. When he came under observation he received a hypodermic injection of quinine. The following day the urine was black. On the same day a few endoglobular amœbæ and pigmented leucocytes were found in the blood. The hæmoglobinuria lasted through November 23rd, 24th, and 25th, and during these days the examination of the blood was negative as regards parasites. On each of these days quinine was given by intravenous injection. The attack terminated after November 25th ; then the usual treatment was followed for two months, since then he enjoyed good health.

CASE 18.—In this case the patient was robust, and had suffered for a long time from malaria, and previous to this, constipation and distension due to sluggishness of liver, were the original complaints. He came under observation on July 22nd, having a high fever and passing reddish black urine, the hæmoglobinuria. In the blood were found parasites with central pigment, fission forms, and young plasmodia without pigment in any notable amount. Injections of quinine were given in the evening. On the morning of July 23rd the fever still continued, and also the hæmoglobinuria. In the blood were found plasmodia in small numbers

without pigment, and others with pigment granules. The fever subsided about noon, but the hæmoglobinuria continued. In the evening plasmodia were still found in the blood. On July 24th the patient was apyretic, and the hæmoglobinuria had also ceased. In the blood, crescent forms only were to be seen; and the patient made a good recovery in due course with morning dose of quinine sheylate and Lithii Benzoite combined with other drugs of liver complaints. He recovered in 6 weeks.

CASE 19.--This fever in this patient began with cold and lasted five days. The patient, a man of 40 years, stated that he had never had such an ailment in his life. One day in the afternoon he felt a chill in his body, and was forced to have recourse to bed. He became insensible at once, perspired during the night, but felt quite well the next morning. The attacks occurred daily. When seen at eight o'clock in the morning, his temperature was 99 F., his abdomen was puffed up with flatulence, and his bowels were constipated. There was tenderness over the limbs, his eyes were congested, and there were some headache and pain in the back, as well as some thirst during the paroxysm. Otherwise he felt quite well in the febrile intervals. Quotidian malarial fever was diagnosed. Half an ounce of the sulphate of magnesium was given at once. The bowels moved five times in the afternoon, and the paroxysm appeared as usual thereafter. He was seen at 8 P.M.; his temperature was 105° F., and he was slightly delirious. Four grains of phenacetine were administered, and this brought down the temperature in two hours. He was then given at once two doses of a mixture consisting of the sulphate of quinine (gr. v), nitrohydrochloric acid (m. v), syrup of orange (ʒi), and water (ʒi) The following day he took four doses of this, as well as at night; and there was no return of the fevers. Next morning his temperature came down to 97° F., he felt very weak; and the mixture was persevered with for three weeks; and then he was free from the relapses.

CASE 20.--This patient, aged 40, in the month of October, complained of febrile attacks every day with chills, and the duration of the illness was six weeks. He was a resident in a village, which, in the rainy season, is flooded by a river which runs around it. It is a very damp, swampy place, and malaria is very prevalent. When seen one afternoon he was found to be shivering with cold, he had a high temperature, and perspired freely during the night, though he felt quite well again in the morning. This occurred every two days. The bowels were not regular—sometimes constipated, sometimes loose. He had a pale-yellow complexion, and when seen during the apyretic intervals, his temperature was 99° F. He was a very well-built man. Neither the liver nor the spleen were very much enlarged Tertian malarial fever was diagnosed, and the patient was given an ounce of Epsom salts at once, and the above-mentioned quinine mixture from the time that he commenced to perspire. It was so arranged that for the first dose he took fifteen grains, and then five grains three times a day.

He made an uninterrupted recovery and usual recommendation, after treatment was followed, he had no relapse.

CASE 21 --A man, aged 35 years, complained of fever, with frequent evacuations of the bowels, of two months' duration. About two years ago he had an attack of malarial fever. His present trouble began with fever and constipation, and quite suddenly diarrhœa set in and lasted for three or four days, his motions being frequent during the day and night. He was placed under suitable treatment for this, but the intestinal phenomena did not abate, in spite also of restricted diet. The bowels moved six or more times in the twenty-four hours. The fæces were found to be very liquid and full of mucus mixed with blood; and the bearing-down and burning sensation during the act were most distressing. He feels feverish in the afternoon and until the early morning, when the condition abates, with slight perspiration each day. The temperature in the morning was subnormal, and the patient was pale and cachectic-looking, thin and weak. The spleen and liver were enlarged, and there was slight tenderness over the left iliac fossa. The abdomen was retracted, the patient was markedly anæmic, and a venous hum was heard in the neck. The heart appeared to be very weak, and the pulse was small and about 85 per minute. For this condition of malarial fever with dysentery two drachms of magnesium sulphate were administered three times a day, and ten grams of sulphate of quinine every morning. The character of the motions now changed, the mucus and blood entirely disappeared therefrom, and only two watery stools were passed in the afternoon, and these not so copious as usual. Rice diet was instituted from the outset, and this with the above-mentioned medicaments, lowered the temperature. The quinine was continued with, and Dover's powder (gr. vii.) with subnitrate of bismuth (gr. x) administered four times a day. In a day or two the bowels ceased their activity, and iron and arsenic were prescribed, the patient being completely recovered in a month.

CASE 22.—A child, aged 2 years, had suffered from fever for a fortnight. He had been healthy before his present illness. One evening it was noticed that the child's body was pale, and the patient seemed to have no energy. Under treatment he did not improve, but became worse and worse. The child was somewhat emaciated when seen, and the temperature in the morning was 100° and 102° F. in the afternoon. The fever abated during the night time, and the forehead was seen to perspire when he was asleep. The conjunctivæ were reverted on the eyelids, seen to be very white. There was no remission in the pyrexia. For this condition of remittent malarial fever a mixture of quinine hydrochlorate (gr. ii), nitrohydrochloric acid (m. ii, vinum ferri (m. v), and chloroform-water (ʒi) was prescribed, of which three doses were ordered to be taken before the temperature rose. In a few days the fever disappeared, and the patient rapidly recovered from its effects.

CASE 23.—This patient, aged 30, complained of fever with slight chills every second day, lasting for one month. He resided in a country place. He had suffered from such attacks some years previously, for which the present writer had treated him. On the present occasion he was suddenly attacked with feverishness and slight chills when walking in the street. He hurried home and went straight to bed covering himself with an abundance of bedclothes. The fever left him during the night after slight perspiration. Next day he felt relieved, but the following day he was attacked again. He then came under medical treatment which, however, did him no good in spite of being for about a month under large doses of quinine He then changed the residence, placed himself under the writer's care in Lucknow. On examination, the liver and spleen were found to be slightly enlarged, and the temperature subnormal during the day. But for a sallowish complexion, he appeared to be in good condition. The patient stated that he was much troubled with constipation. A dose of magnesium sulphate was at once given, and afterwards a mixture, consisting of quinine sulphate (gr. v), nitrohydrochloric acid (m. v), syrup of ginger (3i), and chloroform-water (3ij) for a dose, to be taken after a movement of the bowels, three times a day, when there is no rise of temperature, and after perspiration has occurred, three doses at once. He had one more attack of a very slight nature. The interesting point in this case is that the quinine acted so well after a change of residence, it having formerly failed to act in a very malarious locality. The treatment was continued for six weeks with ordinary dose of quinine and he was no more troubled with relapses.

CASE 24.—An inhabitant of a small village, aged 40, suffered from enlargement of the spleen and fever, of a year's duration. Twelve months previously, he had suffered from cold and fever; the former left him, but he suffers from fever still. The entire abdominal cavity appears to be filled with the splenic tumour. The temperature was 100° in the morning, and 103° in the evening. The patient was pale and cachectic. As stated, the abdomen was enormously enlarged ; and on palpation a hard resistance was met with at the umbilicus. The liver was also enlarged, and the patient had no appetite, a small and frequent pulse, and a weak heart. For this condition of malaria with hypertrophy of the spleen, the usual dose of sulphate of magnesium was given at once, liquor epispasticus was applied over the splenic tumour, and a pill consisting of ten grains of quinine was given every morning, and one of iron, arsenic, and strychnine after meals. A diet of milk and rice was ordered. Five days afterwards, he affirmed that he felt a little better ; and it was seen that the blistering fluid over the splenic tumour had caused a large suppurating wound. The temperature was 99° F. in the morning. The wound was dressed, and took more than two weeks to heal At the end of the second week, it was noticed that the splenic tumour had shrivelled up to the level of the tenth rib ; and the

patient appeared to have undergone a remarkable improvement, eating well, talking cheerfully, and looking very bright. Nevertheless, the blistering fluid was again carefully applied and the splenic tumour speedily disappeared—quite a remarkable experience.

CASE 25.—A married lady, aged 25 years, complained of fever and cough every afternoon, of a month's duration. She had three children and was usually very healthy. Her present illness began with a feeling of slight cold in the tips of the fingers and toes, fever supervening at night, lasting during the latter until the morning when she feels relieved. Now and then she had a hard and dry cough. In the morning her temperature was subnormal, and in the evening 103° F. The pulse was 120 per minute, full and strong. She suffered considerably from headache at this time. Auscultation could discover no thoracic abnormality. The bowels having acted freely, quinine was forthwith administered, and exhibited three times a day before the onset of the paroxysms. In less than a week she had completely recovered. This case was diagnosed and treated by a medical man as Tuberculosis.

CASE 26.—This patient, aged 35 years, had for two weeks suffered from fever on alternate days. He appeared to have had such attacks every year at the same time, this being the third anniversary of the paroxysmal outbreaks. He feels cold and soon afterwards fever supervenes at 10 P.M. and lasts until nine o'clock the following morning, when he perspires freely and feels well all day. The conjunctivæ were slightly yellowish, otherwise, with the exception of constipation, no abnormality could be detected. He was first seen on the afternoon of the day of remission, when the temperature was subnormal and he felt quite well. Five grains of calomel were given at bedtime, and an ounce of magnesium sulphate in the early morning. From this he had a free action of the bowels, and the above-mentioned quinine mixture was administered three times before the paroxysm was due. The attack proved to be only a very slight one, and further seizures were avoided by the continuance of the drug. He was kept on this and sloppy diet for a few more days, and he made an uninterrupted recovery and had no attack after three weeks' medication.

CASE 27—A married lady, aged 27, complained of fever, which is slight in the morning and high in the evening : this appears to have lasted for three weeks. She had never suffered from such a disorder before. She was six months pregnant. The fever sets in during the evening, when her body and eyes feel very hot, and she perspires slightly when asleep. This was the second pregnancy. She was first seen in the morning, when her registration was 100·2° F., and the pulse quick. It was the same, and also the temperature, in the evening ; there was a bitter taste in the mouth and the bowels were inclined to be constipated. Warburg's tincture was prescribed with equal parts of glycerine, the same to be

continued for a week, after which she appeared to have completely recovered and delivered healthy child.

CASE 28.—A maid-servant, aged **25**, complained of fever and headache for three days. For many years she appears to have suffered from the same condition. She felt slight chills in the afternoon, followed by a certain amount of feverishness. During the night she perspired slightly, and felt better in the morning. When seen in the afternoon, the temperature was 104° F., and she complained very bitterly of the excruciating head-ache. Five grains of phenacetine were forthwith administered, which led to copious perspiration and a lowering of the temperature. In the morning she was given a saline aperient, and after this she was prescribed five-grain doses of quinine three times a day. The next day she had a very slight paroxysm, after which the malarial manifestations disappeared.

CASE 29.—A man, aged 35 years, had for two weeks suffered from a continued fever. Except for a bronchial attack some time ago, he appears to have enjoyed permanent good health. Whilst camping in a mala-rious district, he felt suddenly feverish, and was treated for a week, but felt no better. On the morning when first seen his temperature was 100° and 102° F. in the evening. The patient was given to understand that in our climate quinine will not usually exert its specific action until the bowels are moved. It was ascertained that before the temperature rises in the evening he feels slightly cold in the hands and feet, but he could not say that he had noticed any perspiration. A full dose of calomel was given at bedtime, and a liberal quantity of Kutnow's powder in the early morning. After evacua-tion of the bowels, a dose of the quinine mixture was ordered every three hours until the expected time of the paroxysms. The outcome of this was that the temperature in the morning was 100° F., and slight perspiration seemed to have occurred during the night. He was advised to continue the mixture; after two days there was no return of the fever, and by the end of a week the patient had perfectly recovered. After a couple of months he returned to me with relapses and much more aggravated abdominal syptoms; the usual treatment of relapses was adopted and he had not been troubled any more.

CASE 30.—This patient for one month complained of slight feverishness in the evening. Some four years ago he had suffered from malarial fever, which he contracted whilst shooting in the jungle. Under medical treatment he recovered from this. The patient is a largely built man, and plethoric. The morning temperature was normal, that of the evening 100° F. In the afternoons the tips of the fingers and hands become cold, and soon afterwards the feet also. He perspires freely in bed at night, and then he feels relieved. Constipation is inclined to be obstinate. He was ordered a dose, morning and evening, of a mixture of quinine hydro-chlorate (gr. v), nitrohydrochloric acid (m. x), and chloroform-water (ʒi) and half a tumberful of vichy water at meal times. He continued with this

treatment for a fortnight, but did not get better. He was ordered a change of air to a salubrious district, where he speedily recovered under quinine medication.

CASE 31.—A girl, aged 12 years, complained of feeling feverish in the afternoons for three months. She appears to have often suffered from fever, and more particularly during the rainy season. She first feels somewhat cold and then has a burning sensation all over her body, perspiring freely when asleep. When seen, the patient was thin, weak, and much exhausted by the febrile manifestations. The spleen was slightly enlarged. She had been previously treated with the specific remedy elsewhere. The temperature was in the habit of running up to 102°F. in the evening. She was ordered the quinine mixture, to be taken in the apyretic intervals. Under this plan of treatment she got rid of the fever in five days, when she was prescribed a mixture of iron wine (m. x), Fowler's solution, hydrochlorate of quinine (gr. ii), nitrohydrochloric acid (m. iv), syrup of ginger (℥ i), and infusion of gentian (℥ iv), for a dose to be taken after each meal. She persevered with this for two months, and had no more malarial attacks.

CASE 32.—This patient was a boy of 7 years, who for two months suffered from malarial fever. The child was healthy. During the rainy season he was laid up with fever, which did not respond to fever mixtures. On making regular observations in this case, it was noticed that the patient perspired during the night, and that the temperature comes down in the morning. The quinine mixture aforesaid was ordered to be given when the fever was absent, and the fever mixture during the paroxysms. It took six weeks of this form of medication to overcome the disease.

CASE 33.—A man, aged 30, complained of fever, beginning with chills, and of three days' duration. He had had a similar attack a month previously, from which he made a good recovery. He was seen just after the attack, the temperature being 100° F. He said that while he was in the country he felt cold, and soon after the fever developed; he then perspired and felt better. Saline aperients were given at first, and the quinine mixture afterwards. This brought down the temperature; and after a month's specific medication he completely recovered without further attacks.

CASE 34.—This patient was a boy of 10 years, who suffered from continued fever for three months. Prior to the present illness he had been in good health. Three months ago, he felt cold and hot, and perspired every alternate day. For this he received the usual quinine treatment elsewhere without any effect. When seen he appeared to be anæmic; the conjunctivæ were slightly yellowish, and the spleen somewhat enlarged. There was tenderness over the liver, and the bowels were constipated. The morning temperature was 100° and that of the evening 103° F. At 12 A.M. he perspired freely, cooled down, and became hot again and the following mixtures were ordered to be taken: Ammonium chloride (gr. iii), tincture of nux vomica (m. ii), carbonate of magnesia (gr. v), syrup of

rhubarb (3ss), and Inf. chiretta (3i), for a dose ; quinine, vin. ferri and pepsin taken after meals. He recovered in a week, and after treatment was followed.

CASE 35.—This patient was 23 years of age and complained for nine months of enlargement of the spleen and bleeding from the nose. Prior to the present illness he had been in good health. About a year ago he went on a visit to Nepal, where he was attacked with cold and fever and perspiration every alternate day. He left that locality and returned to Lucknow. When seen, his face was very pale and bloodless and yellowish in colour. The abdomen was enormously enlarged, and on palpation a hard tumour was felt as far as the umbilicus filling the left side of the abdominal cavity above. The liver was also enlarged. The temperature in the morning was normal, but in the evening 100° F Epistaxis was present, and malarial cachexia was observed. The patient was given a mixture consisting of sulphate of magnesium (gr. xxx), ammonium chloride (gr v), and tincture of nux-vomica (m. v) ; and every morning quinine. Liquor epispasticus was also applied over the splenic tumour every week on three occasions. By this means both the liver and spleen shrivelled down, and the patient now began to enjoy good health, and in two months he appeared to be quite recovered.

CASE 36.—For four weeks a man, aged 58, had complained of a continued fever, prior to which he had enjoyed good health. The present illness came on very suddenly with chills, perspirations at night, relief being obtained thereafter. The conjunctivæ were jaundiced, there was tenderness over the liver and bowels, and a certain amount of constipation The temperature was 100° in the morning and 103° F. in the evening. Half an ounce of sulphate of magnesium was given at once, and the patient was ordered to take the quinine mixture at the stage of perspiration Next morning the temperature came down to 98°, and the evening fever only attained 101° F. Magnesium sulphate was given in the morning again, and the quinine mixture was directed to be administered as usual Every evening he had a slight rise of temperature, but the treatment was persevered with and mustard was applied over the liver and spleen, enlargement of which gradually yielded and the patient made an excellent recovery.

CASE 37.- This patient was 35 years of age, and resided in a place which becomes flooded during the rainy season, and vegetation abounds He complained of a month's fever and general weakness. About three years ago, he had an attack of the tertian form of malarial fever after returning from a shoot in the jungle. He was treated in the usual way, and recovered in due course. Since then, every three or four months, when he had been away shooting, he had the quotidian form of the disease, which always responded promptly to quinine But gradually his whole system became undermined, and he grew weaker and thinner. During the summer he went to Simla, and there also was attacked with the fever and hill-

diarrhœa afterwards. This made him extremely emaciated ; so that he was obliged to leave the place and visit Naini Tal, where also he had an attack of the fever. But under treatment he rapidly improved. He came to Lucknow in October, and put himself under the usual treatment. He returned to Singahi in the month of February, and was there attacked again. The patient, when seen, was confined to bed, and markedly cachectic His pulse was scarcely perceptible and very weak There was a systolic mitral murmur to be heard, and the liver and spleen were somewhat enlarged. The bowels were very constipated, and could not be moved without the aid of an aperient Every night he had weakening pollutions. The morning temperature was 101° and that of the evening 102° F He had slight perspirations while asleep at night For this cachectic dyscrasia he was prescribed the usual quinine mixture, and then one of ammonium chloride, digitalis, and bitter infusions, twice a day half an hour before each meal, animal food being allowed The quinine was commenced with from the onset of the perspirations. He rapidly improved upon this treatment, the morning temperature falling to 98° F , and the evening to 100°. In a week he was able to take a journey to Lucknow. Here also he continued the same medication. It was noticed that whenever the exhibition of quinine was stopped he had a rise of temperature. *Colonel Anderson* was called in consultation, and he advised five drops of Fowler's solution to be given after each meal and the quinine and ammonium chloride to be abandoned. The result was that the temperature rose again and dyspeptic symptoms became very troublesome. The patient resumed the usual treatment as described in last chapter, and mustard plasters were applied over the liver and spleen. He was emphatically ordered to take a walk every morning, and to have as much nourishing food as possible. In three months' time he appeared to be quite a different man. Since then he has had no recurrence of the fever, in spite of living in a very malarious locality. He complained loss of sexual power for some time afterwards, but it returned to him in due course of time without any special treatment.

CASE 38.—A countryman, aged 25, resident in Lucknow, for three months complained of evening fever. This was his first illness of the kind. It first came on with cold, pyrexia, and perspirations every alternate day, for which he was treated with quinine in the usual way and got better He has slight fever every evening, leaving him after an hour or two without perspiration. He knows exactly when to expect the febrile seizures by the headache, heat of the body, and looseness of the bowels. He is a fairly developed countryman, with yellowish conjunctivæ. The liver and spleen were slightly enlarged. The temperature in the morning is normal, but in the evening 102° F. The pulse is weak and the patient suffers from palpitation. A dose of the ammonium chloride mixture was prescribed for administration in the mornings, and the quinine mixture three times a day, when the temperature falls under 99° F. He followed this plan of

treatment, and after six days said that he did not now suffer from the fever, only the gastro-intestinal troubles. The ammonium chloride mixture was then stopped, and the routine treatment as recommended in the previous chapter was commenced and the patient completely recovered in 6 weeks without being troubled again.

CASE 39 —A native of Lucknow, aged 30, complained of fever for a week, prior to which he had never been ill. Four days ago he felt chills, and his temperature rose in the evening but fell in the morning—such attacks occurring on alternate days. His face was of a lemon-yellow colour, and the conjunctivæ were of the same hue. The morning temperature was 100° F. Nothing abnormal could be discovered in connection with the liver and spleen. An ounce of sulphate of magnesium was given at once, the fever mixture during the paroxysm, and the quinine mixture when the latter had abated. After a free motion of the bowels, the fever came down in the evening to 99° F , and the quinine was given at that time. He had three doses of it the next day, with the result that he gradually felt better, and in due course made a complete recovery and medication was given up. He returned to me after 6 months in quite reduced state of health so much so that his recognition was impossible. He was struggling in such condition of health from last 3 months and had been under various sorts of treatments available in this country. He had been subjected to all sorts of anomalous complaints. He was induced to be put on usual routine treatment and he was spared with splendid recovery in two months.

CASE 40.—A Hindu gentleman, aged 37, resided at Rampore Muthra which is a swampy and damp locality, especially during the rainy season, by which time there is considerable malaria. He complained of cold, fever, and perspirations for a week. The same time last year he had suffered from a similar febrile attack for a period of nine months. The abdomen had become enlarged, and there was œdema of the dorsum of the feet, as well as in the hands and face. He had become very weak ; and the slightest exertion was sufficient to bring on palpitation and faintness. From all this he recovered in one month by aid of the specific remedy. In the present attack he does not suffer so much from chills, and the paroxysms attacked him only on alternate days. By the continuance of my routine treatment he was no more troubled again.

CASE 41.—This patient, a man of 40 years, suffered from malarial manifestations for a few days. His present illness appeared in the form of chills and pyrexia. His temperature was 105°F., and his pulse full, strong and regular. During the hot stage he was given phenacetine, which made him perspire freely in a short time, and his temperature came down to 100·2° F. forthwith. He felt better in the morning, and he was then given a saline aperient, and the usual quinine mixture thereafter. He made an excellent uninterrupted recovery and no further treatment was continued.

·r one month he became victim to it and I was told he died after a few
th's struggle.

CASE 42. —This patient, a man of 30 years, was a resident of Singahi
ch is a damp and extremely malarious place. He had suffered from the
r for six days. Three months previously he had an attack of orchitis,
which he was treated by the present writer. He is very fond of tiger-
sting, which pastime he follows every summer in the jungle of the Nepal
der. He was advised to abandon the shooting this year, as he is so
ilitated as to be very likely to contract malaria. In spite of this warning
vent to shoot in the month of April. He returned to his residence after
·e weeks of hunting, and sent for the writer, who took a day to reach his
ie, which is thirty miles from a railway station. He was found in a state
yperpyrexia, the axillary temperature being 105° F. He was delirious,
d out for water every five minutes, and had dry tongue. He was given
onade to drink. It was ascertained that the attack came on, in the
noon of alternate days, with chills and sudden access of pyrexia ; he per-
es during the night, and feels better in the morning. A grain of phena-
ne and of quinine still further increased the diaphrosis, these drugs
ig administered every half hour. When the temperature came down to
° F., he was given ten grains of quinine, and the dose was repeated in an
r Next morning his temperature was 97° F., and he continued to take
grains of quinine three times a day for three or four days, after which he
·ontinued it. After a month he went to shoot again, and returned in the
ith of June with another attack of malarial fever. When seen, he was
id to be suffering from the same type of the disease as previously ; the
ie kind of treatment as before was instituted, and he was advised to
tinue the quinine for two months and to spend the rainy season on the
s. He persevered with the drug for a week or two, but went to Naini

There also he had an attack of the fever during the rainy season while
·e is much vegetation on the hills. The attacks did not now seem to be
severe as formerly. Since then he had become so accustomed to the
·ase, that he does not regard it seriously. He knows exactly the time he
l suffer from it, and so has become a regular consumer of quinine. In
sequence of his more or less saturation of his system with the drug, the
iperature is now never so high, nor the chills so marked as hitherto.
feels for a short time cold in the tips of the fingers and some general
.ly sensations. The temperature is usually 101° F., during the parox-
is, and he gets better after taking a few doses of quinine. He never
·ears to be able to shake the infection off his system, though he has taken
iine and arsenic for months and months at a time. On one occasion after
febrile seizure his blood was submitted to microscopical examination by
present writer. The malignant parasites were found in the red corpus-
. He went for sea voyage and on return he is careful with all prophylactic
isures and had no more trouble.

CASE 43.—M. H , resident in Lucknow, aged 40, complained of continued fever, with some bilious vomiting, for one week. He had never had malarial fever previously, and is a diabetic subject. He had no chilliness, only feverishness, after which he began to vomit. At 12 P. M. the temperature was 101° and at 6 P.M. 103° F. The vomiting was constant. and the bowels were constipated. He complained of slight headache and lassitude. This bilious remittent form of malarial fever was met with a mixture of liquor ammonii acetatis (ʒi), spiritus ætheris nitrosi (ʒss), syrup auranti (ʒi', and aqua menthæ piperita (ʒi), for a dose every three hours. But this mixture was rejected by the stomach, so that it became necessary to apply mustard plasters over the liver and stomach, for an hour at a time, during the night. He was given five grains of calomel at bedtime, and Epsom salts in the early morning. This led to the free evacuation of the bowels and the reduction of the temperature by one degree in the evening. The following morning his temperature came down to 99° F , when he was given ten grains of quinine dissolved in fresh lime-juice three times a day. He seemed quite better in a few days, and he was then ordered a tonic consisting of the citrate of iron and quinine, nux vomica, and nitrohydrochloric acid—a dose every morning during convalescence.

CASE 44.—This patient was a male servant, aged 23, who had suffered from fever and enlargement of the spleen for five months. About ten years ago he had been similarly afflicted ; since then, up to the present illness, he appears to have enjoyed good health. About five months ago he went to Calcutta, where he had an attack of fever, which used to come on every afternoon, with a feeling of chilliness followed by perspiration. He affirms that the fever used to leave him under medical treatment, but as soon as he abandoned the medicine it returned. He did not improve under treatment which he underwent in Calcutta, and he suffers from fever and looseness of the bowels ; he had an attack of dysentery about a month ago. His appearance is very cachectic, the liver was slightly enlarged, and the spleen markedly so The temperature in the morning was 99° and in the evening 101° F. His pulse was fairly good. For this condition of malarial cachexia a drachm of sulphate of magnesium was given every morning, quinine twice a day, and arsenic after meals. Liquor epispasticus was applied over the spleen. The patient made an excellent recovery.

CASE 45.—The patient, a Hindu girl of 16 years, for two months complained of fever with cold sweats. Before that date she had been in good health. The illness began with shivering and cold, which lasted an hour at a time, and was followed by profuse sweating at night She felt better in the morning. After a few hours the paroxysms returned. At first the fever used to come on every alternate day, but for the last two or three weeks it was of daily occurrence. The bowels were moved about six or seven times in the day. She complains of giddiness and nausea. When she came to Lucknow for special treatment she appeared to be a cheerful

well-nourished girl. The liver and spleen were not markedly enlarged. The morning temperature was normal, and that in the evening 102° F. ; the pulse was fairly good. A drachm of magnesium sulphate was administered in the early morning and ten grains of quinine during the sweating stage— the latter to be continued in doses of five grains three times a day thereafter. In two days she reported no return of the fever nor of the headache, and the bowels were now quite regular. The treatment was given up afterwards. After a month she began to have the relapses. After 6 months she returned to me in cachectic appearance. She was put under ordinary treatment and continued up to two months. She was no more troubled after this treatment.

PART II.

The Etiology, Pathology, Prophylaxis, Symptomotology and Treatment of Beri-beri.

CHAPTER I.

ETIOLOGY.

General consideration — Beri-beri—which is an affection that I regard as an endemic or epidemic form of peripheral neuritis of uncertain origin, but occurring particularly in those subsisting on rice in warm countries in the midst of unfavourable conditions of sanitation,—is of causation as mooted as its clinical manifestations are protean. Opinions, some of them as ridiculous as vague, have been propounded by writers of no little celebrity, these giving undue weight to certain factors at the expense of others. Thus has the already-existing confusion been augmented rather than diminished, and it would seem that even now, we are little nearer than hitherto to the solution of the etiological problem and the nosological characteristics of the disease.

It is therefore necessary to pass rapidly in review the more important of the various theories that have been from time to time advanced, and see in how far they may be relied upon to explain the salient features of this affection as here and elsewhere observed.

Let us first of all consider the more important of the *predisposing causes*, commencing with that of

Age.—I have not often met with beri-beri in young children and very old persons, though some other writers have had quite the opposite experience. In the epidemic at Reunion

in 1897, for example, the affection was said to manifest itself amongst individuals of every age, and not infrequently seemed to have a sort of preference for the elderly subjects of atheromatous arteries. On the other hand, in a certain ship epidemic of which I have information, no one under fifteen years of age was attacked, and there were over fifty on board. In another epidemic of the kind, fifty-five children who were passengers escaped, whereas the majority of the crew showed signs of beri-beri. Again, we read that the disease took hold upon the pupils of the college of Caraca, Brazil, who were over fifteen years of age, but refrained from troubling all those there under, even though occupying the same room. It would also appear that in 1889-90 the beri-beri deaths in Rio de Janeiro amounted to 830, of which the age-distribution was as follows : —

Age.			Number attacked.
1—7	...	...	2
8—15	...	...	11
15—35	...	...	466
35—55	...	...	285
Over 50	...	...	57
Unknown	...	...	9

From the above and numerous other observations we may conclude that the most susceptible age for the occurrence of beri-beri is from fifteen to thirty-five.

Sex.—Males seem to be more predisposed to beri-beri than females, and the proportion of the former attacked to the latter Simmons places at 27 to 1, for Japan. The medical practitioners of that country incline to the opinion that this is entirely due to the diet, and in Rio de Janeiro, where from 1889-90 there were 830 deaths, the sexual difference in question (720 males to 110 females) is put down to the fact that beri-beri is more commonly observed amongst soldiers and sailors, elsewhere in Brazil the same number of men and women civilians being attacked.

Nevertheless, as with other etiological factors, there is no absolute rule as regards the one we are at present considering, and even the numerous writers on the subject are at variance thereon Pregnant women frequently fall victims to the disease, which in these persons assumes a serious form—the more so when faced with difficult labour.

The disposition to the disease on the part of women is well exemplified in the case of the Singapore Prison described by Sir Patrick Manson, in which institution—female and male prisoners being accommodated—the male side was severely affected by beri-beri, whereas the female side entirely escaped. It is further remarkable that the two sides were dieted alike, the only peculiarity of the situation being that the female side was dry and the male side damp.

Race.—Though beri-beri might be held to be independent of race when occurring in the tropics, it is a well-known fact that in countries having a mixed populace the natives are attacked with greater facility than others. The immigrant coloured natives seem to become victims to the malady more readily than the whites, so that for the latter an immunity has been affirmed, which is sometimes striking, though by no means absolute. But some who have given great study to the disease contend that there is no racial immunity to beri-beri, and point to the fact that the so-called immune whites can contract the disease quite well whenever exposed to it under the same conditions as those who appear to be specially predisposed to it.

In this country it is to be seen sometimes in individuals of all races and every nationality, which fact would seem to indicate that beri-beri is independent of both conditions, the prevalence of the affection amongst the coloured races being probably due to the privations under which they exist.

Occupation —I do not think that any special predisposing influence can be claimed for profession or occupation, as I have observed beri-beri in all classes of society in the

presence of suitable conditions. Some authors maintain that sedentary occupations predispose to the disease, and they point to the number of prisoners and other members of the community attacked under conditions of inaction, confinement, over-crowding, and unfavourable hygienic surroundings. Here it is the poverty of the individuals and the circumstances just named that so strongly operate in the etiological sense, placing them under the worst conditions for resisting the inroads of the disease.

Physical condition.—Some writers hold that the state of nutrition must have a lot to do with the incidence of beri-beri, muscular and robust persons being particularly prone to the disease. " It is a singular fact," says Manson, " and one contrary to what obtains in many other diseases, that the robust and well nourished seem to be more liable to beri-beri than the feeble and half-starved." And he also remarks: " My own impression is that beri-beri attacks any one irrespective of his physical condition, just as measles and small-pox do." I myself am inclined to this latter opinion, and I find that observations in Brazil and elsewhere thoroughly confirm it, though debilitating influences, various kinds of excesses, overwork, and existing diseases would, of course, render the patient more liable to attack, in the sense of lowering the vital resistance to this or any other affection.

Pregnancy and the puerperal condition.—I have already alluded to the susceptibility of pregnant women to beri-beri; and the affection would seem by no means infrequent also during the puerperium. We have it on no less high an authority than Bentley that: " A very peculiar fact, and one which I am quite unable to account for, is the susceptibility of women after child-birth to be attacked by beri-beri." Silva Lima, who found 10 of his 23 parturient women affected, concludes that the " most remarkable inference to be drawn from these statistical data is that the puer-

peral state is one of the most frequent predispositions to the paralytic form of the disease." According to Pacifico Pereira, no less than 31 out of 52 cases could the same be affirmed.

It would further appear that the disastrous influence of the disease in pregnant women is apparent in the frequency of abortion and the serious forms of cardiac affection both in the mother and the dead fœtus. The mortality amongst children who survive is sometimes alarming.

Heredity.—I have been unable to convince myself of the possibility of beri-beri being an hereditary disease, as certain writers have affirmed. It is true, of course, that the children of sufferers from the disease may become so debilitated as to render them liable to attack, and so present a high mortality—the more so as the milk in these cases is oftentimes of an unsatisfactory condition, being deficient in both salts and fatty matter.

Temperament.—In former times the existence of a sanguine, lymphatic, bilious or nervous temperament was given a more or less urgent etiological rôle in this disease, but we now know that these factors are without influence, and can be assigned merely an historical interest in the nosology of the affection.

The comparative frequency of the incidence of beri-beri in the case of sufferers from *tuberculosis, measles, small-pox, typhoid fever, scorbutus, dysentery, scarlatina, syphilis,* and other acute and debilitating affections is well known; and Corre would have it that beri-beri exhibits a marked preference for drunken individuals. It is particularly in the case of convalescents from acute infectious diseases, perhaps, that beri-beri is so frequently observed; and there is a certain peculiarity in this fact, in that the debilitation of the constitution, the anæmia, and the anomalies of nutrition thereby occasioned would in this case not necessarily seem responsible, for beri-beri is comparatively infrequent in the subjects of chlorosis, leucocythæmia, and other conditions of bodily

depression. The question has been carefully investigated by Nina Rodrigues, of Bahia, who concludes that the inter-current manifestation of beri-beri is predisposed to by the existence of a latent *neuritis* of the same nature as that which Pitres and Vaillard observed in tuberculous and typhoid fever patients. He brings forward substantial statistics, which in the main agree with those of Scheube dealing with the complications of this disease which are most commonly observed. The idea of beri-beri being most frequent during the convalescence from the affections alluded to is not far-fetched, for this period is one of polyneuritis or of an undue vulnerability of the nervous system ; and the more plausible the theory becomes when we endeavour on that ground to explain the frequency of beri-beri in chronic alcoholics, in puerperal women, and in persons who have already suffered from beri-beri. A *previous attack* must be considered as a predisposing cause, owing to the frequency with which this factor obtains.

Geographical location.—It is well known that there are certain endemic centres of beri-beri—residence in which renders an individual liable to an attack, though not necessarily certain to experience one—which are to be found in the tropical and subtropical zones of the Eastern and Western Hemispheres. Although it is encountered in or near the tropics, it is now and then met with in remote districts, and is undoubtedly becoming more and more widespread every year, on account perhaps of the capability of the disease principle for being transported to any suitable locality by human beings.

Let us now consider the various parts of the globe where the affection has been from time to time observed. Comparatively speaking, there is not a great deal of beri-beri in *India ;* and it is principally in the rice-manipulating districts of Bengal that it is to be found, though cases are now and then encountered elsewhere. It is more or less endemic mongst the rice-eating Madras soldiers. In the Bengal

and Madras and other Indian prisons the affection is very
seldom nowadays manifested, for therein only the winter
and not the autumn rice is consumed, only paddy at least
three months "seasoned" being cured. This is in marked
contrast to the frequency of the disease amongst these pri-
soners prior to the time that the consumption of the uncured
rice was forbidden. In such populated centres as Calcutta beri-
beri is now more or less merely a sporadic affection, having
lost its former endemic character; and it is curious to find
that the millions of rice-eating inhabitants of Bengal virtu-
ally escape its ravages. According to Barry, in Rangoon,
the incidence of beri-beri is mostly upon the Indian coolies
from the south, that is to say, those who in their native habit
are next thing to immune; and our author concludes that
their morbidity in Rangoon is probably due to their exces-
sive indulgence in rice-kanji, $i e$., the liquor remaining after
the rice has been boiled, and one that is therefore impure.
Other writers agree in the main with his opinion. Braddon
points to this fact as confirmatory of the theory of rice-pro-
duction which he so ably elaborates in his book on " The
Cause and Prevention of Beri-Beri ; " and he tells us that it is
not essential that the vehicle of the disease principle should
be either plain or fermented rice liquor. According to him,
these persons (the Tamils) "who get beri-beri in Rangoon
are natives who leave India in large numbers annually to
assist in the rice-harvest in Burma. This immigration
takes place in September In an account of the circum-
stances of these coolies in the ' Notes and Statistics of the
Hospitals and Dispensaries for Burma for 1889,' the writer—
Leslie—states that there is no privation among them, and that
it is generally from nine months to one and a half years after
arrival in the country that they succumb, first to fever, and
then to beri-beri. Now, these immigrants are independent.
It does not appear that they are looked after by contractors
or large employers, or in any way cared for or provided

with special food and management by legislation, as are the Tamil immigrants into the Straits Settlements. It follows that they subsist on their own means, that is to say, on the cheapest food that they can procure, which is naturally the rice of the country as sold in the shops, *i.e.*, in uncured state. Their food is, in fact, precisely the sort upon which, when they are fed, even in the British Malayan Settlement, as happens in the gaols and asylums, they acquire beri-beri." He further adds that the occurrence of the disease "varies with the sort of rice eaten."

Beri-beri is always to be observed in *Burma* and *Siam*, and has been prevalent there ever since the British military epidemic of 1824. It is also common enough in *Singapore*, where Russell tells us that, from May 1875 to the corresponding month in 1880, there were 1,174 cases in the prisons.

We have knowledge of its occurrence in *Penang*, the islands off the *Cochin China* littoral (especially Pulo-Condor), *Annam* and *Tongking*. I do not think that it is nowadays common in *Siam*. In 1892, the prisoners at *Bangkok* exhibited a high morbidity and mortality. It is seldom seen in an epidemic few in *Tongking* and *Annam*.

One of the most important endemic centres of beri-beri is *Japan*. It is widely distributed over the Japanese islands, though to a less extent perhaps than on the mainland, Hondo, and more particularly in over-crowded, damp, low-lying, and large cities and towns. The endemicity of beri-beri in Japan has long been known, though prior to the middle of the eighteenth century it would seem to have been a comparatively rare affection. Scheube dates the more important epidemics back to 1740 ; and it would seem that these prevailed principally in Tokyo and Kioto, from whence they extended to the various large centres of population throughout the country   In Kioto, from 1875 to 1879 —when the population was 299,000—2,273 were attacked by beri-beri, and 1.093 in 1878. In 1877 no less than 14 per cent of the Japanese

troops suffered from the disease, the percentage in the following year, amongst the same class of individuals, being as high as 38. At the present time I understand that beri-beri is prevalent principally in Yokohama and Osaka, though it is said to be more or less endemic along the west coast and from Nagasaki in the south to Kodato in the north.

Beri-beri is somewhat less common in *China* than in Japan, being now mainly observed in Foochow, Formosa, Wenchow, Soochow, Shanghai, Amoy, Fatshan, Swatow, and Hongkong, the latter place being specially conspicuous for a maliganant epidemic in 1888-89, there being also another outbreak of formidable proportions in 1899 with a mortality of 197 Chinese, the acme of mortality being reached in October, November, and December. The Swatow epidemic of 1895 is not likely to fade from the memory of the inhabitants, and it seems that the people of Chinkiang have become quite accustomed to the summer epidemics of beri-beri amongst them.

From this, as well as from other evidence to the same effect recorded, it would appear that beri-beri is not so uncommon in China as was formerly—and is perhaps now by certain writers—supposed ; and even in such cities of India as Calcutta the disease not infrequently exhibits a marked preference in its incidence for the Chinese quarters.

Nor is beri-beri unknown in *Korea*, though it is still comparatively uncommon there, but gives me the impression of being on the increase since the late war It is principally observed in the southern districts.

It is a well-known fact that beri-beri is one of the diseases most commonly encountered in the *Malay Archipelago* and *Peninsula* ; but nevertheless its incidence there shows annual variations, being in some years very great and in others, comparatively speaking, the reverse. In some of the islands it is pandemic, but such localities as Sumatra— where the Dutch troops exhibited an enormous mortality from it

during the war in Acheen—it is said to manifest itself in epidemic form periodically. There was a severe epidemic in the Straits Settlement in 1895, and in the following year the hospitals there contained no less than 2,057 beri-beri patients, in the next two years the respective figures being 2,058 and 1,329. It appears also that the year 1898 was marked by a virulent epidemic amongst the population of the Singapore gaol, there being 124 attacked, and this after a freedom from the disease from 1885—97 and only two cases during the previous 13 years and the same small number in 1897.

Beri-beri is now endemic in Lampong and along the east coast of Sumatra, and I find that this is also true as regards the islands of Billiton, Banca, and Bintang, it being probably just as common on the littoral of Sambas in Borneo, Sampit, Bandjermassing, Labuna, and in the Sintang mining districts.

Fifty years ago, beri-beri would seem to have been unknown in Java, though it is now there by no means infrequently observed, especially common being the affection also at Batavia, Onrust, Banjuwangi, Celebes, Macassar, Moluccas, Amboina, Saparna, Banda, in New Guinea, and on the southern littoral of Ceram.

Beri-beri is very common nowadays in certain parts of *Brazil* where Dr. Patterson first observed it in 1866, though it is said that the affection was known to the people of Bahia three years previously, though not at the time recognised as such. It thereafter seemed to acquire an extensive distribution and attracted universal attention, with the results that several publications appeared dealing with its protean manifestations. On referring to these, we find that beri-beri was a disease of the country before Patterson's observation, though escaping diagnosis; and it is affirmed that it was epidemic in the state of Minas—at Marianna and Diamantia—from 1858 to 1873. After having broken out in Bahia in 1863, it very soon spread to cities further north, *e.g.*, Para, as an epidemic, and settled down to an endemic rôle in due

course. From Espirito, Sancto, Rio de Janeiro, San Paulo, Parano, and Santo Catherina we have special reports of its virulence; and it is stated from its littoral limitations it extended into the interior, being particularly rife in Alto Amazonas, the Bahian States, Rio de Janeiro, San Paulo, Minas, Matto Grosso, etc. It appears also that beri-beri decimated the Brazilian troops at Humayta and Curuzu during the war between that country and Paraguay. A map showing the morbidity from the affection in Brazil in colour would give the special incidence of beri-beri as extending from Alto Amazonas along the Atlantic littoral to Rio de Janeiro, with sporadic epidemicity from the latter to Santo Catherina—the manifestations of the disease being also marked in the interior of the states in the centre and north of the country.

Regarding *South America*, it would appear that beri-beri is far from common, especially in the states bordering on the shores of the Pacific Ocean.

I am not aware that beri-beri has ever become endemic in *Jamaica* and *Trinidad*, though now and then a sporadic case is observed.

Beri-beri is only occasionally seen in the *French Antilles* amongst the Negroes and Chinese, the affection being known as the "Maladie des Sucreries." It is said to have attacked the Negroes imported from the Congo, in 1859, after their arrival at Gaudeloupe.

The year 1873 saw a great outbreak of beri-beri in *Cuba*, there being a large mortality amongst the Negroes it reaching from 60 to 75 per cent at Palmira.

Prior to 1865, the disease was unknown in *Cyenne*; it then prevailed in endemic form amongst the troops, disappeared for twelve years, and returned to take place as a more or less common affection.

During the American War in the *Philippines*, beri-beri was frequently observed amongst the troops, and sporadic cases are still observed in that locality.

The fishermen on the coast of *North America* now and then suffer from a form of peripheral neuritis which has many features in common with beri-beri; it is, however, not common.

In the year 1898, the island of *Ascension* was the seat of a pandemic of beri-beri, though it had probably existed there in sporadic form previously.

Beri-beri is now and then observed in *St. Helena*, there being no less than 13 cases in 1897 and 8 in the following year, the respective deaths being 8 and 1. The Boer prisoners suffered much from the disease at the beginning of the present century.

The disease is less often observed in *Africa* than in Brazil and elsewhere, being noticed at places far distant from one another. It seems to have become more plentiful within recent years, being now and then observed in Natal at Pietermaritzburg; in West Africa on the Tanga Coast; in East Africa at Zanzibar; at Senegal, Goree, Sierra Leone, the natives of the Belgian Congo, Togo, Niger, Soudan, Cameroon, Gaboon, Loanga, and Angola. At one time beri-beri was known only at Mauritius (amongst the British soldiers), Reunion (epidemic in 1805, 1821, 1838, and 1847), and on the island of Noissi-Be off the north-west Madagascar coast, though we are told that it was prevalent in Madagascar, in the village of Diego Suarez, in 1866-67. There is said, in 1878 and 1879, to have been imported to Mauritius from Assam and Lower Bengal a peculiar form of dropsical disease attended by anæmic symptoms, but which, however, in its marked infectivity and low mortality and absence of paralysis, did not correspond to beri-beri as we know it.

Meteorological factors.—Manson, Simmons, Gayet, and other authorities have claimed for beri-beri an amenability to season in the respect of cold and damp and the opposite conditions. Though high temperature and damp undoubtedly do favour the development of germs, I refuse to subscribe to the theory of the incidence of this

disease being dependent upon meteorological influences. The latter, however, would seem to affect the initial occurrence of the affection in Japan and subtropical localities and where the malady is so common, it raging all the year, but with summer and autumn maxima of morbidity in these regions. I am unable to explain how these influences operate, and also which of them does so most vigorously ; but I do know that heat and moisture are observed in all beri-beri centres, and presume therefrom that they are essential to its occurrence. For instance, in Brazil beri-beri exhibits a periodicity of prevalence, *i.e* , with maximum incidence at the end of summer, with its great heat and dampness, and minimum in winter and spring, in districts which are remote from the coast and at a considerable altitude and have, despite their intra-tropical location, a relatively low mean annual temperature.

Climate.—I do not look upon the temperature of a locality as having the importance hitherto attached to it in the production of beri-beri, although it may have something to do with the evolution of the disease when once implanted in a patient, the latter being perhaps somewhat unfavourably affected by thermic extremes The old idea of beri-beri being peculiar to tropical or subtropical countries is gradually becoming abandoned, and for the reason that it is year by year manifesting itself sporadically in temperate climates, being now and then observed in even cold ones.

Although there have been some who have denied that the so-called beri-beri of temperate climates is the same as that observed in endemic centres elsewhere, I am convinced as to the inaccuracy of this affirmation, and the more so after consideration of the histories of the various manifestations of the disease in, as it were, virgin soil.

The reason for the malady taking on this tendency to invade new regions would seem to be owing to the increasing

facilities for human intercourse—in former times but little existing—and commerce, the affection gaining a footing in this place or that owing to certain contingent factors favourable thereto, *e.g.*, *racial predisposition, dirt, poverty, overcrowding, defects in hygiene*, and so forth.

In view of the ravages of beri-beri in certain tropical and subtropical countries, there are many in temperate climates who have asked if the time will come when the affection will become as virulent amongst them as it has been and is in its original location. I do not think it ever will, and for the reason that the sanitary conditions in temperate climates are becoming more and more ideal and the intelligence and nosological precautions of the people more and more acute and practical. Thus, many cases of ships having arrived at British and other ports with beri-beri patients on board have been recorded, but, so far as I am aware, without the same ever having been known to infect the populace, and the restricted occurrence of the affection in asylums in temperate climates may also be cited, *e.g.*, the Dublin Asylum. The disease is incapable of spontaneous generation anywhere, and it can only occur in ships and places of the kind just named after the casual agent of the disease has been brought thereto by some infected person. So it comes that the theories of orological, alimentary, malarial, or the like origination are far-fetched and devoid of foundation in fact.

Thus I regard also Walker's hypothesis of the causation of beri-beri by worms, this being suggested by his frequent observation of these intestinal parasites in such patients. We read in his report to the Budapest Congress that no less than 756 cases had the ankylostoma duodenalis, 284 the tricocephalus, 155 the acaris lumbricoides, 123 the oxyuris vermicularis, 2 the distoma, and 24 miscellaneous species; and it would seem that both he and his followers regarded the first-mentioned as the principal factor in the occurrence of the disease, this idea receiving a certain amount of support

from the coincidence of the affection with the known distribu-
tion of the parasites in question. Nevertheless, if we come
to examine all the circumstances very closely, we shall find
that the geographical distribution of the disease and the worm
are not precisely the same, and also that it is not infrequently
the case that where the former exists the latter does not, and
vice versâ. It is quite unnecessary to adduce instances, for
that the fact obtained is undoubted.

There have been some who have incriminated *fish* for the
production of beri-beri, the dry form of various species being
held responsible for the lodgment of the germ of the disease,
or, in the opinion of others, a worm which lives in them. The
advocates of this theory point to the fact that in certain
endemic centres a considerable quantity of desiccated fish is
consumed by the people. Still, it is also true that the disease
occurs in localities where fish is not a part of the dietary
and also in prisons where this also obtains.

One of the theories which has had, and still perhaps has,
a plethora of advocates is that of the causation of beri-beri
by *rice* amongst people who make that cereal the basis of
their support. Here, again, it may be mentioned that the
affection is not infrequently observed amongst individuals in
whom the contrary obtains, *e.g.*, in certain parts of Brazil.
Much has been written regarding the alleged production of
beri-beri by the ingestion of decorticated rice, that is to say,
the white variety deprived of its pericarp and proteid layer,
and in a stale condition, the poisoning thus becoming existent
after decortication but not before. The poison thus produced
is held to be of the nature of ptomaine poisoning. This is
said to be the outcome of the formation of ferments or *enzymes*
acting only in solution, and the product of a specific fungus
in stale rice. It is the peripheral nerves that are specially
concerned in the morbid process resulting.

Eijkmann has closely studied the manifestations of beri-
beri amongst numerous prisoners in the Dutch Indies with

special reference to this theory ; and he holds that the grain contains a poison acting in the way named, but contained in the seed itself and not in the coverings. He has made a series of interesting experiments on fowls, with a view to confirm his theory of the poison being peculiar to the rice seed and separate from the whole grain or raw paddy, and of the natural antidote to the seed poison being in the coverings of the grain ; and he was able to produce a form of peripheral neuritis in these fowls by feeding them only on decorticated white rice, but never when he made them exclusively consume the grain partly covered by its pericarp—the red rice--or on paddy or whole rice. No matter what the source of the rice, the fowls made a satisfactory recovery from this disease, which resembled beri-beri in its pathological anatomy, symptomatology, and irregularity of evolution, in due course when he changed the white rice for the red variety or when he added husks or pericarp to the former. This theory of the poisonous character of the grain and the antidotal nature of its coverings, as investigated by this observer, has been much criticised and the accuracy of his methods and the general technique of his experiments impugned.

The 1897 epidemic of Poulo Condore is one of the observations that has been adduced in opposition to such theories as that of Eijkmann, where the prisoners, being fed on the kind of rice that in the terms of this theory should be innocuous, suffered severely from beri-beri.

Travers also objects to the rice theory after having observed in three institutions in Salangor, all supplied with identical rice from the same source, a severe outbreak of beri-beri in one and no sign of the disease in the other two. This inconsistency Braddon explains on the ground of the relative quantity of rice consumed, it being less, he says, in the institutions that escaped the disease

Ellis also refuses to subscribe to the rice theory after an observation in 1900 of the disease on a steamer en voyage

from Singapore to Australia, on board of which there was a crew of 28 Malays and 51 Chinese. " All," he says, " were fed on Siam rice, cooked in the same manner, and in one galley. When in cold weather, near New Zealand, beri-beri broke out in the starboard forecastle, inhabited by 14 of the Malays, and in all there were 8 cases and 5 deaths. This forecastle had the galley situated immediately after, with but a thin wooden partition. The heat from the galley caused the cabin to be always sweating and steaming as it was some-what wet from the bad weather experienced at the time, and, in fact, converted into a perfect incubating chamber." After remarking that no food was eaten, or stored, in this place ; he says that disinfection was carried out at his instigation, with the result that the disease was checked ; and he adds that had " the rice been in fault, it is difficult to understand why the eight cases occurring should have all been among fourteen men occupying one cabin, and that the remaining hands should have entirely escaped." The same author narrates another experience concerning an outbreak of the disease amongst some lunatics fed according to European ideas. It appears that, in 1890, he " separated twenty healthy native patients on admis-sion in two cottage blocks, giving them European food, and no rice whatever. At that time, though beri-beri was very pre-valent amongst the natives, we had never had any case among Europeans or Eurasians, and I wondered if in any way the food was in fault. My experiment had to be given up in less than three months, as more than half of the cases had by then developed symptoms of the disease. The opinion I then came to was that beri-beri was a place-disease, that the soil and buildings were infected, and that people dwelling there were liable to absorb the poison, whatever it was, that this absorbed in sufficient quantity was the cause of beri-beri, and this opinion I have never seen reason to change "

Various writers have regarded beri-beri as a form of poisoning by *arsenic*, particularly amongst the workers in

certain mines, minute doses of the metal being capable of producing certain suggestive symptoms. But analyses of the urine of beri-berics have not always shown even a trace of arsenic : beri-beri has not been observed amongst certain mountaineering people who habitually consume the drug, and the latter is actually a safe and salutary treatment for the very disease which it is supposed by the advocates of this theory to cause. The hypothesis may then be dismissed forthwith as untenable

Defect in *nitrogen* is one of the numerous other theories that have been advanced to account for the occurrence of beri-beri, and has had a great vogue in Japan and elsewhere. The case of the Japanese Navy has often been cited in support of this nitrogen-starvation theory, it being insisted that, from a beri-beri morbidity of one-fourth of the sailors previously existing, the affection is now next thing to unknown amongst them ; and this, too, since the addition of more nitrogenous elements to the dietary. Nevertheless, I regard this great improvement as due to rearrangement of the hygienic conditions on up-to-date lines of perfection, and so far as amplitude of nitrogen is concerned, as a mere coincidence. The theory cannot explain the restriction of the disease to certain houses in the midst of communities all fed alike, the occurrence of beri-beri amongst both the poor and the affluent classes of society, and such other factors as the geographical prevalence of epidemics. The idea is well illustrated by the Singapore Prison epidemic, in which both the male and female sides were fed alike and consumed the same water, and yet the former class suffered severely, located as they were under conditions of dampness, and the latter entirely escaped the beri-beri.

Let us now consider the *microbic origin of beri-beri*, a view of production of the disease that is being supported by an ever-increasing array of observers.

The theory of *infection by a telluric miasm or toxin* is one that has been fathered especially by Sir Patrick

Manson, who holds that beri-beri is occasioned by the absorption by man of a saprophytic organism from the earth, interior of houses, etc., and that in this manner, and after the style of the alcoholic disease, there is produced in time a peripheral neuritis. "The soil," he says, " is the infecting medium ; the man residing on it is poisoned, not infected. In the case of alcoholic neuritis—so like beri-beri—the germ of the disease is the yeast plant ; the culture medium, the saccharine solution ; the toxin, the alcohol. The alcoholic germ may be swallowed with immunity ; not so the toxin which it generates. So with beri-beri : its germ lives in the soil ; it produces some toxin there ; and this toxin, being inhaled or swallowed by man, produces in him a specific neuritis ; and, just as man can carry the yeast plant from one place to another, so may he carry the beri-beri germ. So far as I have been able to interpret them, this is the only hypothesis which fits in with all the facts of the case "

This is, of course, a mere theory by our author advanced without substantiative evidence ; and there have been some who have affirmed that if the germ of beri-beri lives in the soil those who walk on it with sores on their feet would be more affected than others who do not. This has been observed occurring in natives by Reacur, who also emphasises the frequency of the disease in those having operation wounds on their bodies, i.e., surgical beri-beri.

Hamilton Wright holds that beri-beri is caused by a germ which in some way or other gets into the system, and then gives rise to morbid processes, particularly in the pyloric and duodenal regions ; in this way a toxin is produced which exerts a malign influence on both the efferent and afferent peripheral nerves, the central nervous system being secondarily affected. This germ may be expelled from the body of the host with the motions, and so infect the soil, houses, furniture, and other appurtenances of the poverty-

stricken unclean ; it may also get into water or be carried
about by dust, although the organism perishes rapidly under
the influence of light, thus accounting for the localised out-
breaks in prisons, mines, and other dark places where the
vital conditions are favourable.   He refuses to subscribe to
the rice theory, in spite of the numerous facts that have been
advanced in support of it.

The next theory that falls to our consideration is that of
infection by a pathogenic micro-organism, the same existing in
the blood, cerebro-spinal fluid, etc.   Though numerous
microbes have been discovered, there are several observers
who have failed to discover any after the most painstaking
investigation.   Amongst those who have obtained positive
results may be mentioned Lacerta, Pereira, Segan, etc., as
well as Fajardo who has discovered a hæmatozoon in the
circulation, and Glogner who found a plasmodium like that of
malarial fever in the corpuscles.   His organism, obtained by
splenic puncture in 63 out of 78 cases, proved to be an oval
body possessed of a nucleus and mobility, in size about a
tenth less than that of a red blood corpuscle.

During a particular epidemic Chantemesse and Ramond
isolated a germ, which bore a close resemblance to the *pro-
teus vulgaris*, from the blood and cerebro-spinal fluid of beri-
berics ; this they were able to cultivate, and after inoculation
reproduce the disease in laboratory animals.   There are
some, however, that maintain that the cases were really
those of beri-beri, but of some other simulating affection.

Pekelharing and Winckler are observers who have made
some interesting investigations into the pathology of the
blood in beri-beri, and they are said to have found in
the circulation of individuals, even in health apparently, in
beri-beri centres certain micro-organisms which readily stain
with fuchsin.   These cocci were capable of reproducing the
disease in animals, and the histological findings in the nerves
thereof were undoubtedly suggestive of that affection.

Rost claims to have found a diplococcus, like the tubercle bacillus in appearance, in damaged rice, rice-water, blood, and cerebro-spinal fluid of beri-berics; and it seems that this can be cultivated on the usual media, give tinctorial reactions and reproduce a beri-beric affection in some of the lower animals.

Dubruel also testifies to the presence of a sporulated bacillus in the system of beri-berics as directly provocative of the disease, and proves by a series of investigations that it can give rise to the affection in fowls, monkeys, etc.

It may also be noted that some insist that the casual agent of beri-beri must pass through the bodies of certain species of insects before it can become operative on mankind.

Whatever may be the casual agent of beri-beri, it certainly finds a most convenient vehicle of propagation in rice, and is fostered by the unsanitary surroundings amidst which the majority of the tropical and subtropical consumers of that cereal exist. This I affirm in spite of the objection urged against rice propagation by those who make much of the fact that cooking of the grain destroys both the germ and its toxin, to which I reply that amongst the Indians the cooking of the rice is but imperfectly performed in many instances. Furthermore, the fact that beri-beri occurs in countries in which rice is not the staple article of diet must surely be exceptional when compared with its prevalence in regions in which the people mainly exist upon that grain. Where rice is not so thoroughly cooked, beri-beri would probably be much more common than it is, even there.

Finally, I hold that beri-beri is caused by a *specific micro-organism* (the exact nature of which is at present unknown) which is mainly transported by rice (or other food-stuffs in an imperfect condition), and is especially apt to reproduce the disease in individuals circumstanced amidst sanitary or hygienic defects, particularly poverty, *dirt* and *starvation.*

CHAPTER II

PATHOLOGY.

Appearance of the cadaver.—This will depend upon the form that the disease has taken during life. Thus, there will be an almost entire absence of fat in the dry and atrophic cases; whereas, in the wet cases, the microscopical phenomena will be somewhat similar to those encountered in individuals who have died from some dropsical renal affection. In this case there will be a considerable amount of serous liquid in the subcutaneous connective tissue and between the muscles.

Cases of sudden and painful death, as from respiratory or cardiac paralysis, will manifest the agony in the features—the face being swollen and cyanosed, the mouth open, the lips frothy, the eyes protruding from the head, the conjunctivæ ecchymosed, and the jugular veins very prominent.

Rigor mortis is usually of short duration and slight in degree, and the post-mortem lividity is manifested very soon after the lethal issue.

Pericardium.—No matter whether œdema elsewhere exists, the pericardium is practically always in a dropsical condition, the effusion being in variable quantity though usually not sufficient to seriously compromise the action of the heart, perhaps not more than a drachm.

The interior of the membrane presents a glazed appearance, and ecchymoses may sometimes be observed on the exterior.

Heart.—I have seldom or never seen this normal in beri-beric cases, the usual condition being dilatation or hypertrophy of the right ventrical, but seldom increase in size of the left. A blackish, fluid clot containing blood usually distends the right heart and the large vessels at the root.

We have it on the authority of Ellis that, in 125 cases, the average weight of the heart in beri-berics was a fraction over 13 ounces, but less than 9 ounces in 204 others.

Although murmurs are discoverable on auscultation during life, one is oftentimes struck with the entire absence of any autopsical evidence after death, the valves not giving way under the water-test due probably to the post-mortem retraction of the heart.

Fatty degeneration and opacity of the muscular fibres of the myocardium are nearly always to be observed in these cases ; and signs of myocarditic inflammation may be seen in patches as in various other infectious diseases Evidences of myocardial hæmorrhage may likewise be forthcoming. The microscope shows effacement of the muscular striæ in the affected fibres.

Blood.—The pathology of the blood has been the subject of investigation by Quincke, Fajardo, and many other observers. According to these observers, its reaction is acid, and its appearance blackish, fluid, and sticky. It does not clot well, and readily escapes on opening a vessel. This retardation of coagulation is said to be due to the large quantity of carbonic acid which it contains. The corpuscular content is diminished, and the discs deformed ; the hæmoglobin is also diminished. Such substances as cholesterine may be found in the blood in abundance, and the liquid itself presents alterations suggestive of the occurrence of a toxæmia.

Lymph.—This presents no suggestive abnormalities.

Lungs.—The lungs are usually distended with blood, and they may be found in an œdematous condition with apical and anterior emphysema.

Pleural effusion may be observed, though generally not to a great degree, and the membrane itself may show signs of extensive ecchymosis.

Intestines.—In addition to congestion of the *stomach* and small hæmorrhages in the organ, the intestines usually

present punctiform bleedings and may be in an œdematous condition.

Innumerable parasites may be found in the bowels, but, as these are so common in tropical countries, etc., and in no way characteristic of beri-beri, it is quite unnecessary to enumerate them.

Liver and spleen.—Although these organs may show in occasional cases a certain amount of congestion and fatty degeneration, such lesions cannot be considered as either constant or characteristic of beri-beri ; and I do not attach to them the importance that some writers have claimed.

Kidneys.—Hyperæmia, cloudy swelling, and granular degeneration of the renal substance are not infrequently observed ; the pelves of the organ may show signs of hæmorrhage and the kidney may be in a state of inflammation. In such cases the cause is not improbably other than beri-beri.

Nervous system.—By far the most important and interesting of the nervous lesions in beri-beri are to be found in the *peripheral nerves*, and it is these that should first be looked to for autopsical confirmation of the existence of the disease. Numerous degenerated fibres are to be observed amongst the healthy ones ; and the former appear to be increased in size, has its myelin sheath irregular in its contour, and gives the impression of segmentation. There is a deficiency of the medullary substance at the level of Ranvier's nodes, and the myelin seems to have undergone disintegration into a granular material. Closer examination will show that there may exist a few nuclei at the level of the interannular nuclei, where the nerve trunk is reduced to the empty sheath of Schwann owing to the disappearance of the myelin there together with the axis cylinder. Besides this, there may occur a thinning of the fibres with swellings here and there in the neighbourhood of the latter, there being located darkish globules in the midst of a frothy material

stainable a pinkish colour with carmine. The sheath of Schwann collapses owing to the disappearance of the myelin, though the former may show fine fibrils in its interior. There may sometimes be observed proliferation of the nuclei of the endoneurium and congestion of its vessels ; and in slowly progressed cases the endoneurium may be in a gelatinous hyperplastic condition. The connective tissue undergoes augmentation between the bundles of nerve fibres, so that the latter may be divided into bunches by these bands. No regularity of distribution can be assigned to these lesions, for both sound and diseased fibres may be observed in the same bundle, and the degree of the morbid process may vary at different places and intervals.

The *spinal cord* may also show changes, especially softening in the lower third and at the level of the two enlargements, as might be suspected from the occurrence of limb troubles during the life of the patient. The anterior and posterior spinal nerve roots may show signs of degeneration and of ecchymoses.

There is usually a marked increase in the amount of the *cerebro-spinal fluid*, as will be readily appreciated on opening the cranial cavity and vertebral canal. In the opinion of certain observers this is a constant feature of beri-beri. This suggests the desirability of lumbar puncture during life for the relief of the symptoms, and has good foundation in fact.

The *brain* may show milky hæmorrhages, and meningeal hyperæmia and adhesions may also be noted in acute cases.

Muscles.—Muscular degeneration, atrophy, or hypertrophy are often to be found in the paralytic cases. In the case of the second-mentioned lesion, the muscles, when considerably affected, will be of a yellowish colour, with a yellowish and pinkish marbling alternating in the hypertrophic cases. Scheube holds that the muscles are nearly always in a state of atrophy with increase of the nuclei and fatty degeneration of the fibres. In some cases there may

be a sort of colloid degeneration, compressing the fibres and making them become attenuated and homogeneous.   In time they may be completely transformed into a colloid material, with the subsequent formation of nucleated connective or fibrous tissue.

Generative system.—The semen and the secretion of the glands of Bartholin and Littre remain unaltered in beri-beri, in spite perhaps of the disorder of the sexual function.

Osseous system.—The bones, cartilages, etc., present no lesions peculiar to beri-beri.

CHAPTER III.

SYMPTOMATOLOGY.

Amongst the principal symptoms of this disease in its various clinical forms may be mentioned œdema of legs, loss of knee-jerks, hyperæsthesia, anæsthesia, wasting of muscles, paresis, and a host of other ailments. It is best studied by studying the complicated symptoms under separate heads, the functions of which are severally affected.

Nervous system.—*Sensory functions.* The earliest symptoms under this head is impairment of common sensations, following this are the numbness of legs to a variable extent, hyperæsthesia in one part, delayed sensation to blunt or sharp instrument in other part, tenderness on pressure on the calves of the legs, and over the nerve trunks. There are feelings of various other sensations, for example of pricking of needles, aching, smarting, burning. The hyperæsthesia and paræsthesia lead to complete anæsthesia and these changes appear sooner in the lower than the upper extremities. Particularly they appear over the skin of the front of the tibia, the dorsi of the feet and the sides of thighs.

Reflex.—The knee-jerk is completely gone at the very commencement of the disease, and as a rule all deep reflexes are lost.

Motor functions.—The earliest change in the motor functions is the weakness of the legs specially at the knee-joint, and the majority of the patient come and complain that they get exhausted in walking much sooner than before. He perceives the weakness at first in the legs and on examination the muscles of the calves and gastrocnemii are observed to be thin and flabby and if squeezed against the underlying bones the patient will shriek out with pain and draw the limb away. Then it is noticed that the hand grasp is also deficient and the foot muscles are affected. At first it

begins with paresis but progresses on rapidly to absolute paralysis and at the same time it is brought to notice that those muscles are wasting. If tested with Galvanic and Faradic battery the excitability is diminished. On the advance of the disease the paralysis may become general and it is most evident in the extensors of legs and hands. Hence *ankle-drop*, *foot-drop* and *wrist-drop* are the characteristic features of beri-beri. When the patient is asked to walk, his gait is peculiar as in ataxia, and on attempting to turn round he becomes unsteady. If the patient endeavours to raise his legs he is hardly able to do so and also incapable of crossing them or of placing one foot on the top of the other. In very advanced cases the abdominal and intercostal muscles and diaphragm are paralysed.

Nutritive functions.—The wasting of the muscular tissue cannot be estimated at first, but as the paresis advances the atrophy of the muscles progresses in the same order as the paralysis. Hence the leg muscles waste first and then Thenor and Hypothenor and then the muscles of the arms.

Vaso-motor function.—The mechanism of Vaso-motor function is disturbed due to effusion of serous fluid. There is general anasarca of the body so that the patient is lodged in a water-bed. The commencement of œdema begins from the surface of the shin and then the face, giving a puffy appearance to the patient, and then the attention is drawn to his complaint. The effusion takes place in the serous cavities as well as in the subcutaneous tissues, producing extensive ascites, hydrothorax, and hydropericardium, and lastly the lungs are attacked giving rise to crisis of dyspnœa. The skin and mucous surface are extremely pale and the extremities are cold, and owing to the constriction of the peripheral arteries the pulse may be extremely small and thready while the heart appears to be beating forcibly.

Circulatory system.—Palpitation of the heart is an early symptom; the heart is quickened on slightest exertion and

on inspection the impulse is diffuse, the epigastric pulsation is perceptible and apex beat is displaced outward. Above all there is violent throb on both sides of the neck (" Crotid throb") which is very peculiar to this disease, and that throbbing is sometimes so troublesome that it renders the patient very uncomfortable. On percussion the dullness of pericardial area is enlarged more to the right side ; and on auscultation the systolic bruit is heard with reduplication of the second sound, and the diastolic pause is shortened. There is evidence of dilatation of right side of the heart having pulmonary systolic murmur very audibly heard. Severe cases exhibit the heart beating more frequent and irregular in rhythm ending in syncope.

Respiratory system.—The attack of dyspnœa constantly occurs and cough with frothy, watery and profuse expectoration, sometimes tinged with blood, is the frequent complaint. Cynocis and embarrassment of breathing due to œdema of the lungs are often the signs of fatal issue.

Digestive system.—There may be a complaint of constipation or symptoms of dyspepsia ; vomiting during the course of the disease is considered to be a threatening sign of death.

Urinary system.—The quantity of urine is diminished, the patient passes very scant urine, very dark in colour and of a low specific gravity, and it contains no albumen or blood, and at the fatal issue urine is suppressed. These distinctive features of urine distinguish beri-beri from Bright's disease.

The clinical types of the disease.—A great many forms of beri-beri have been contributed, but the forms which appear more commonly impressing themselves most forcibly on our senses are only mentioned here :—

    1. The atrophic or dry beri-beri.

    2. The œdematous or wet or dropsical beri-beri.

    3. The mixed beri-beri.

    4. The acute pernicious beri-beri.

All these classifications are arbitrary as one form may suddenly or slowly merge into another.

1. **The atrophic beri-beri.**—One can easily imagine the picture of this form of beri-beri as the patient is a mere skeleton with wrinkled skin accompanied with other characteristic symptoms of the disease.

2. **The œdematous beri-beri.**—The patient swells beyond recognition, his face bloated, the eyes almost closed owing to the dropsy of the upper and lower lids. The whole face and head are enlarged, almost circular in form. The arms puff out and become circular, the elbows rounded, the wrist immovable from the forearms; the fingers as large as sausages; the thorax and abdomen shapeless and much enlarged. The legs are puffed similarly as the arms; the dorsi of feet are tense with fluid. The most remarkable features in this form of the disease are the deep grooves noticeable in places of pressure that are made by pillows and bed. Breathing and pulse are rapid, and in an advance case, dyspnœa is very distressing.

3. **The mixed beri-beri.**—This form of the disease is the combination of the first two. That is to say, there is œdema to some extent, particularly in the pretibial region and feet and there is numbness of the shins, there is muscular wasting and tenderness of the calves' muscles. There is no knee-jerk; there is murmur in the heart with dilatation on the right side. The urine is scant, containing no albumen.

4. **The acute pernicious beri-beri**—May occur in any type of the disease at any time in the course of a case and is frequently observed in the dropsical type. The grave symptoms appear suddenly bringing about a rapid termination of life.

Diagnosis.—The diagnosis of beri-beri is not usually difficult, if one keeps in mind the chief signs, for example, muscular atrophy, anæsthesia, hyperæsthesia, tenderness of the calf muscles, peritibial swelling. " Crotid throb," scant

urine without albumen, absence of knee-jerk, lastly foot-drop or wrist-drop. There are diseases which bear very close resemblance to beri-beri, namely, multiple and peripheral neuritis, and alcoholic and chronic arsenical peripheral neuritis and epidemic dropsy.

Peripheral neuritis.—In neuritis the muscular atrophy and peritibial swelling and tenderness of calf muscles never occur and in a case due to alcohol there are tremors and deficient memory ; in arsenical neuritis there is coryza, pigmentation of the skin and hoarseness. Moreover in both alcoholic and arsenical neuritis the left side of the heart becomes dilated, whereas in beri-beri the right side is affected and there is a distinct history of arsenical and alcoholic poisoning.

Epidemic dropsy.—This disease has some similarity to beri-beri, therefore a confusion may arise in the minds of the inexperienced in diagnosing beri-beri. The searching clinical observation tells us that epidemic dropsy is characterised by a sudden appearance of general anasarca, preceded by fever and diarrhœa, while in beri-beri the œdema is gradual and no fever and diarrhœa and the genitals are not affected. There is irritation of skin often accompanied by rash and it is absent in beri-beri. There is a pronounced anæmia and none in beri-beri. The paresis and anæsthesia are never found in this disease or they may be very slight due to mechanical pressure and they are prominent features of beri-beri. The knee-jerk is lost in beri-beri from the very commencement, whereas in epidemic dropsy sometimes it is exaggerated or may be lost somewhat due to effusion of fluid in the lower limbs. The urine in the last stage of epidemic dropsy shows Indican reaction while of beri-beri presents dark colour, scant, no albumen. The crotid throb is the great diagnostic distinction of beri-beri and is found invariably in all cases.

Prognosis.—The mortality varies according to the stage of the disease or circumstances of the surroundings of

individuals. It is from 5 to 10 per cent.   It is a very lingering disease lasting for a long time, and the peculiarity of the disease is that the patient under suitable treatment begins to get better, so much so that all his relations are satisfied and solaced when all of a sudden he gets a relapse under the same régime of treatment and eventually dies.   It is very wonderful how rapidly it may come on, and how rapidly it proves fatal.   An absolute favourable prognosis ought not to be ventured so long as the patient is in the endemic area, and so long as the disease shows a tendency to be active. The appearance of grave signs like crotid throb, dilatation of heart, epigastric pulsation, rapid feeble pulse, cynosis, cold extremities, dyspnœa, paralysis of diaphragm, and of the intercostal muscles, extensive œdema, suppressed urine, make the prognosis very unfavourable.

CHAPTER IV.

PROPHYLAXIS.

There are several methods of combating beri-beri, of which the following is a brief narrative : —

Change of residence.—This is very important, and the only form of prevention that some believe in. It is equally effective in the case of a person already attacked, the improvement in the patient's condition being oftentimes next thing to marvellous.

In the event of removal being impossible, the room should be well ventilated, and the general sanitation of the dwelling enquired into, with special reference to damp, dirt and soil-pollution ; and preference should be given to an upper storey of the house or higher levelled building.

Fresh air and non-fatiguing exercise are in all cases strongly indicated when the same can be indulged in.

Bacterial Prophylaxis.—This comprises both the *disinfection* of the house and the soil upon which it stands. It is based upon the microbic origin of the disease, and in not a few instances the procedure has been followed by very satisfactory results. Any of the ordinary efficacious disinfectants may be used, such as corrosive sublimate, particular attention being paid to the furniture and everything that may be opened to suspicion of infection. Before the removal of the patient, all his clothes and belongings should be disinfected, and if this be properly done, the chances of his infecting others are reduced to a minimum. In short, we must consider him as vehicles of contagion, just as in small-pox, etc., and act accordingly on the usual aseptic, antiseptic and hygienic lines. Mosquito curtains should be used, in case the poison of the disease may be carried by these insects, and all swamps in the neighbourhood should be done away with, in case the miasmata arising therefrom should impair the vitality of the

individual. All ailing persons should be promptly isolated to prevent the possibility of their infecting others. Bathing and personal cleanliness are to be commended under all circumstances.

Regimen.—This specially concerns the diet, which should be made ideal and as suited to the circumstances of the individual as possible. This is particularly the case as regards rice; and what I have already said regarding the alleged dangers of that vehicle of infection will suggest the lines on which its supervision should run. It should certainly, and without exception, be well cooked and given as hot as possible. The impure varieties of the grain should always be avoided. The utensil in which rice is boiled should be carefully kept covered.

CHAPTER V.

TREATMENT.

There is no specific remedy for the disease—dieting, nursing, hygienic and symptomatic measures being the essence of the conduct of any given case.

Diet.—As in other affections, the diet of the beri-beric is of considerable importance. It should be as nutritious as is compatible with its digestibility. It should comprise a liberal amount of nitrogenous, fatty, and albuminous material, and be thoroughly cooked. The alleged origination of the disease in nitrogen-starvation is not without significance. The food should approach the European standard in as far as is consistent with the climatic conditions under which the patient exists. Dyspeptic and other alimentary troubles will, of course, call for modifications on general principles in accordance with indications.

Drugs.—As already stated I know of no drug that will cure beri-beri, though some of them are not without influence in relieving urgent symptoms.

For the elimination of the bacterial toxin, such purgatives as *sulphate of soda, croton oil, sulphate of magnesium, and calomel* may be tried; and in certain cases they will be found not unsatisfactory.

Benzoate of soda is an efficient internal antiseptic, and in the opinion of Bucholtz will arrest the development of the micro-organisms which he considers of etiological interpretation.

No matter what may be the indication, it is absolutely necessary that the treatment be commenced at the earliest possible date after the initiation of the disease.

Venesection.—The letting of about half a pint of blood is useful in acute cases of beri-beri—the more so as it allows of the elimination of a certain amount of toxic material and

opposes œdematous tendencies, especially as regards the lungs The jugular or median cephalic veins may be operated upon. The results are sometimes surprising in their alleviation of the urgent symptoms, but the procedure is one that I do not recommend as a routine measure, but only to meet pressing indications. This procedure is invariably performed in this country by the Hakeems.

Some have recommended the letting of blood directly from the right side of the heart, in the event of the above-mentioned procedure being ineffective. It is certainly a heroic method, and one that can be countenanced only under desperate circumstances.

Blood lavage has also been advocated for its heart-tonic properties.

Saline injections.—In cases of flagging circulation, these may be tried, but the results are apt to be disappointing.

Symptomatic treatment.—The various symptoms arising from affection of this or that system of organ must be treated as they arise, and by so doing the general and local condition of the patient may not infrequently be considerably improved. Let us now consider briefly a few of the more important instances, leaving the others to be manipulated on the ordinary lines :—

Cardiac troubles.—The condition of the heart must be watched in all cases of beri-beri : otherwise the patient may rapidly succumb to the intensity of the affection.

Digitalis is the remedy of remedies in these cases ; it may be exhibited in the form of the tincture, the infusion, or of digitaline ; and will then favourably influence the palpitation, dropsy, and other troubles of cardiac origin. In dropsical cases it is as well to combine it with some such diuretic as squills or acetate of potassium.

In cases of threatening heart failure a prompt stimulant, as strychnine, caffeine, alcohol and nitroglycerine or amyl nitrite may be called for. Cocaine has been tried in these

cases, and is said to have tonic effect upon the heart, and ergotine may be expected to have the effect of allaying the congestions arising from disorder of that organ; and there are many who prefer strophanthus for long continued cases in preference to any other remedy. I have found 1 per cent solution of nitro-glycerine in a drop dose every 15 minutes very efficacious in relieving the symptoms of " crotid throb " which is sometimes very distressing to the patient. Oxygen inhalation is also very valuable in cardiac troubles.

The diet is, of course, very important also in beri-beri cases; and it should be of as nutritious a kind as possible consistent with efficient digestion. Rice diet should be abandoned altogether, animal and wheat flour be substituted.

The patient must have perfect rest in bed during the severity of the morbid manifestations, and Oertel's method is one to be commended in cases of valvular trouble.

I have seen iodide of potassium prove of service in chronic heart cases, its stimulating and eliminative effects being not rarely very marked.

Some writers propose to inject the extract of the supra-renal capsules, with a view to the stimulation of nutrition and the elimination of the toxins of the disease. I understand that encouraging results have been forthcoming from this procedure.

Treatment of the nervous affections. —Various measures have been recommended for the treatment of the beri-beri neuritis, such as electricity, strychnine, and other nervine tonics.

Electricity has not always proved of service in my hands. The Faradic current may be applied to the affected parts, though the procedure is not without the risk of unfavourably influencing the existing degeneration.

Strychnine, however, is much more satisfactory in cases of beri-beri paralysis. It has no specific effect, but its general tonic and recuperative effects may be utilised.

The method of lumbar puncture has been warmly advocated by Lé Dantee and others, especially in chronic cases. In view of what I have already said of the increase of the cerebro-spinal fluid, the method is, theoretically at least, well founded. It is of service in urgent cases also of intracranial pressure, and it is of favourable influence upon the action of the heart and tends to diminish congestions· It is sometimes surprising how the somnolence of the patient changes for intelligence and alertness after the operation.

I am not in favour of mercurial injections, except in early cases. When the disease has become chronic, they are apt to do more harm than good and augment the existing neuritis.

Blisters over the lower end of the spine may assist in causing resolution of the nerve trouble, but in acute cases they are apt to aggravate it.

I have no faith in injections of tincture of iodine, as proposed by certain authors.

Quinine is useful as a tonic, especially should the patient have a malarial taint to be residing in a malarial district.

Amongst other measures which have been advised for the relief of beri-beri paralysis may be mentioned camphor, cinnamon, and peppermint, and also hydrotherapy.

The application of general principles and the exhibition of the orthodox medicaments will be called for in the presence of such other troubles as *laryngitis, bed-sores, dyspepsia, diarrhœa, fever, headache, vomiting, œdema, etc.*

CHAPTER VI.

OBSERVATION.

CASE I.—A Mahomedan gentleman, aged 40 years, an inhabitant of Chatgam, came to Lucknow for treatment. He was a stoutly built individual, and seems to have been ailing for the last three months.

I examined him and found such degree of general anasarca that he had the greatest difficulty in breathing. The dyspnœa and palpitation were so distressing that he was almost insensible.

There was a great increase of dulness on the right side of the heart; the urine was scanty and of a smoky appearance, but contained neither albumin, sugar, blood, nor casts, and had a high specific gravity.

There was slight paresis of the lower limbs and an area of hyper-æsthesia; but there was loss of tactile sensibility, as he felt the pressure of the tip of my little finger.

There was pulsation of the jugular veins in the neck, and the knee-jerk seemed to be entirely abolished.

I ascertained from his relations that he was very fond of rice, and that he passes most of his time in the villages to look after his zemindari affairs.

The treatment in this case consisted in prohibition of rice-eating and prescribing an entirely meat diet, especially birds. He was given strophanthus, caffeine citrate, strychnine, and nitro-glycerine at intervals. He made a good recovery and returned to his native locality. I was subsequently informed that, shortly after settling down there, he had another severe attack from which he ultimately died.

CASE II.—A Mahomedan gentleman, residing in Lucknow, aged 55 years, had for the last nine months complained of indisposition. He had occupied a house in a very damp and congested quarter, and his dwelling certainly showed signs of undue moisture. I ascertained that he was a great rice-consumer, and had lived almost entirely on the grain for the last ten years.

On examination I found a marked degree of dropsy. The lungs were very œdematous and gave rise to a distressing cough.

The urine was dark in colour, scanty, non-albuminous, of high specific gravity, but contained neither casts nor blood.

There was wrist-drop and pain in the part on deep pressure. Pulsation could be observed in the neck.

His voice seemed to be of impaired tone; and from the semi conscious condition when first seen he never recovered, dying on the fourth day of treatment.

CASE III.—I was called to see a sailor resident in Noakhali in Bengal At the time of examination he was propped up in bed, presenting intense dyspnœa, cyanosis of the tips of the fingers, and lips, and considerable emaciation, especially of the face.

Diarrhœa and constipation seemed to alternate, and he could move neither his arms nor legs.

The urine was almost entirely suppressed, only a very small quantity being voided once a day.

The œdematous condition of the body was really enormous in degree, especially about the lower limbs, abdomen, and chest.

The fæces were voided involuntarily in his almost unconscious condition; and he died two days after being first seen, and this in spite of the usual medicaments assiduously prescribed

CASE IV.—Whilst staying with the District Judge of Noakhali, I was requested to see one of his servants who was the mali of the garden

He was about 35 years of age and had been ill for three or four weeks with what he described as slight fever and constipation

Œdema of the limbs and body developed after a short time, so he was unable to walk about.

On examination I found rapid action of the heart, pretibial swelling, slight swelling of the abdomen, loss of the knee-jerk, tenderness on pressure over the calves of the legs, and a slight amount of paralysis of the legs considerably impairing flexion and extension of the members. The lower limbs were also in a numb condition

He passed urine in my presence, but only a very small quantity. It was dark in colour, and contained neither albumin, casts, nor blood

His case was diagnosed as one of early beri-beri, and he was sent away to the hospital forthwith.

CASE V.—Some time ago, a civil surgeon of Noakhali accorded me the privilege of obtaining material for clinical study at his hospital, as he and I were old college friends and on very friendly terms.

One of the interesting cases that I saw was a man of 40 years, who had been indisposed for the last three months. The illness in question commenced in the rainy season, at the time when he was a coolie and purely a rice-eater.

He had general dropsy and difficulty in breathing, as well as dulness on the right side of the heart extending over nearly the whole of the epigastrium and up over the left border of the sternum beyond its usual limits. There was marked pulsation in the neck, *i.e.*, " carotid throb."

The urine was almost suppressed, he was passing only about an ounce or two once a day. It was of a very smoky colour, had a high specific gravity, but contained neither albumin, casts, nor blood.

There was difficulty of articulation, the attempts at phonation producing a husky tone of the voice.

He could not move his lower limbs at all ; the right hand was paralysed, and he could with difficulty put forth his left one to take food or medicine. Sensibility in the limbs was considerably impaired, and there the œdema was much firmer than elsewhere. The knee-jerk was abolished, and constipation alternated with diarrhœa.

The patient died three days after admission to hospital. The civil surgeon conducted the autopsy in my presence. On opening the thorax, we found a great effusion of serous fluid from the lungs. pleura, and pericardium. There was a great dilatation of the right heart in both cavities, and hypertrophy of the left side of the organ was in an hypertrophic condition The blood seemed to have accumulated in the great veins and lungs, as well as in the right chambers of the heart. There was œdema of the cellular tissues, and an enormous peritoneal effusion was observed.

CASE VI. A native of Noakhali, aged 30 years, and a sailor on one of the ships, having neither syphilis nor a neurotic family taint, had sailed a lot in China where his food consisted mainly of rice He had suffered from febrile troubles for a month before being seen for the first time.

On examination the principal symptoms were numbness and weakness of the hands and legs, together with " drop-wrist" and " drop-foot," inability to walk, and abolition of the knee-jerks. He was pale and anæmic, and had some œdema of the legs and tenderness of the calves He was unable to take a firm grasp of my hand, and I observed a carotid throb.

I prescribed strychnine and iron, and continued the exhibition of these drugs for a month, and changed the treatment for a general tone therapy and he recovered in due course.

CASE VII.—One of the native residents in the village district of Noakhali was sent to me for treatment by a medical friend, who said that his patient had been ill for a month, and quite unable to work.

His symptoms were drop-foot, abolition of the knee-jerks, inability to walk, anæmia, œdema of the legs, weakness and numbness and tenderness of the hands and feet, and exquisite tenderness of the calves. Palpitation was also a distressing phenomenon in this case.

He was given strychnine and iron with satisfactory result.

CASE VIII.—A gentleman, resident in the district of Fareedpore in Bengal, came to Lucknow for treatment, especially for the method of Hakeem, as the place is more or less noted for the oriental procedure. He brought a letter of introduction from one of my friends, so that I was able to see him as soon as he arrived.

He seemed to be about 35 years of age, and of thin build. He gave as personal history that he had been ill for the last three months, at first complaining of fever and weakness, afterwards noticing some loss of power in his legs and trembling in his gait. Gradually the front of the shins became swollen, paralysis of the lower limbs developed, locomotion · became

extremely difficult, and the slightest exertion gave rise to palpitation and dyspnœa.

His case was diagnosed as beri-beri by the doctor in his native place, but the treatment instituted by him proved so ineffective that he came to Lucknow for further advice.

Though I did not then make a searching examination, I had no difficulty in observing that he had general dropsy, that the abdomen was greatly enlarged, the chest increased in size, the face puffy, dyspnœa present on the slightest exertion, and the legs and hands much swollen.

He put himself under Hakeem's treatment, and remained so for a month, during which time he made satisfactory progress. But all at once he became worse, and was again brought under close observation.

The symptoms now appeared to be very much aggravated ; and in addition to those previously noted the distressing attacks of dyspnœa and also pulsation in the neck (carotid throb). He passed urine in my presence to the extent of only one or two ounces. It proved to be very dark in colour and of high specific gravity, but contained neither albumin nor blood.

The paralysis of the legs and arms was not complete, that is to say, when I held the limb up he could retain it in position. The œdema of the legs and abdomen was very great. The pulse was feeble and frequent, and the breathing was very much hampered and effected with great physical exertion.

A murmur could be heard in the mitral area, and the heart itself was greatly dilated. The apex beat was displaced, and pulsation of the organ could be observed in the epigastrium.

General tactile sensibility was considerably impaired.

I placed the patient on a diet of nitrogenous food, excluded starchy substances therefrom. He was also prescribed Fowler's solution of arsenic after meals, and a diuretic mixture of digitalis and caffeine three times a day. Nitro-glycerine was specially ordered for the dyspnœic attacks. He was recommended to take electric baths and at all times to wear warm garments next the skin.

He seemed to improve much under this treatment, the dropsy almost entirely disappearing and so much bodily strength returning that he was able to take carriage exercise. Unfortunately, and very suddenly, he had one day to return home, where he had another attack and died.

CASE IX. —A man, aged about 30 years, and of the servant class, sought my advice as he had been ill for a month with weakness of the limbs and palpitation.

I found on examination that he could walk properly. There was slight swelling over the tibia and anæsthesia over the dorsum of the foot. He resented handling of the calves owing to the tenderness there existing. The knee-jerk was absent, the gait was staggering, and it was easy to make out

epigastric pulsation. Carotid throb and a mitral systolic bruit were present, the patient experienced palpitation on exertion, and dilatation of the heart was discovered.

Strychnine and strophanthus were prescribed, and the patient recovered in due course.

CASE X. – A gentleman, aged 40, consulted me at Patna. He had spent a great deal of his life in Eastern Bengal and Assam.

He complained of weakness and swelling of the legs, which had commenced six or seven weeks ago. His trouble started whilst he was in Assam, at first suffering from fever and gradually losing the power of his legs.

On examination I found œdema on the front of the legs, anæsthesia over that area, and an abolition of the knee-jerks and drop-foot, the same preventing him from taking walking exercise.

The urine was scanty, but there was no œdema about the abdomen of chest.

The dilatation of the right side of the heart was discovered, and there were breathlessness and palpitation on slight exertion.

I prescribed the liniments of ammonia and of mustard for massage of the legs, and strychnine and arsenic internally; and under these and other medicaments as from time to time indicated he eventually made a satisfactory recovery.

CASE XI – A gentleman, aged 40, consulted me about three years ago whilst I was visiting a village in the district of Malda in Bengal.

He complained of weakness of the legs, inability to walk, and breathlessness. There was no syphilitic history His work was such that he had to pass a good deal of his time in the damp places, and his food consisted mainly of rice. He noticed at first some swelling and weakness of the legs, as well as experiencing palpitation of the heart.

On examination I found that his knee-jerks were absent, his calves very tender to pressure, tactile sensibility abolished, and his muscles very much relaxed. He says that he has almost lost the power in his ankles, and he is unable to walk without support.

Strychnine and arsenic pills were prescribed as well as friction over the legs with some stimulating liniment of the kind already described, and a change of air. He greatly surprised me by recovering in the comparatively short space of a month.

CASE XII.—A gentleman, aged 45, consulted me some time ago in Patna, and stated that he had been all his life in different parts of Eastern Bengal. It appears that he had first noticed weakness in the legs and palpitation of the heart on exertion. Gradually this weakness increased so much that he had to remain quiet, and he also noticed a sensation of tingling in his legs.

On examination I found absence of the knee-jerks, swelling of the shins of both legs, great pain on handling the calves, and a poor appreciation of pin-pricks on the dorsum of the feet

The urine was normal, but the right side of the heart was dilated.

I prescribed the usual medicaments, but he refused to take them as I was compelled to leave the place for a week or so. After my return the patient sent for me again, and I was greatly surprised to find that his condition was so much worse I found him propped up in bed and presenting general dropsy. The abdomen was enormously enlarged, the thorax was swollen, and the feet were highly œdematous and very much more so than the legs. He had cyanosis and intense dyspnœa and air-hunger. The throbbing of the carotids also occasioned the patient considerable annoyance. The urine was suppressed.

I tapped the abdomen, and obtained about two gallons of ascitic fluid. Oxygen was administered for a period of ten hours. He took nourishment in the liquid form, beef-tea and various nutritious soups constituting the dietary of the patient. He was also prescribed the usual medicaments according to existing indications.

Although I tapped the abdomen twice, he made very slow progress. In time, however, he was able to walk a little and to go out for a drive. He continued to be treated thus for two or three months whilst I was away elsewhere. After a long time I heard that he had suddenly had a relapse, with speedy death, after six months of my treatment,

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